

**Genetic Testing Outcomes in a Utilization Management Genetic Counseling Clinic
Compared to Genetic Testing Ordered by Non-Genetics Providers**

by

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Abstract

UPMC Children's Hospital of Pittsburgh started the Genetic Testing Clinic (GTC) in January 2018. The GTC is a genetic counseling-only clinic that offers same-day and advance-scheduled appointments for referrals from non-genetic providers ordering a genetic test. This clinic is unique in that it incorporates utilization management (UM) for the requested genetic test while providing comprehensive genetic counseling. After one year and 459 patients, outcomes of the clinic, such as test order modifications, family history risk assessment and triage, and genetic test uptake were assessed. Upon IRB approval, retrospective chart review of the electronic medical record and internal databases were performed for 206 of the GTC patients to obtain detailed outcomes of the clinic. Additionally, chart review of genetic testing completed by non-genetics providers prior to the GTC's inception in 2017 was performed for a comparison. Chart review identified 14.6% (30/206) of the GTC patients had unrelated family history risk factors, for which a referral to cancer genetics or cardiogenetics was provided and 7.3% (15/206) of GTC patients had their test modified based upon genetic counselor review. Finally, review of possible results, risks, benefits and limitations of genetic testing were discussed and documented routinely for GTC patients. In contrast, non-genetics providers often lacked documentation of the informed consent process. 77/150 (51%) of the non-genetics providers did not document any of the possible types of genetic testing results, 67/150 (45%) documented one type of possible genetic testing result; 112/150

(75%) did not document any risks, benefits or limitations; and 149/150 (99%) did not document the possibility of incidental findings. Genetic counseling is valuable for patients undergoing genetic testing; however, not every patient receives genetic counseling. This clinic represents a service delivery model that provides genetic counseling and UM for patients who may not have otherwise received it. This has public health significance as it improves access to genetic counseling services, ensures comprehensive pre- and post- test counseling, and has improved insurance authorization approval.

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Preface

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Abbreviations

Frequently Used Abbreviations

ACMG = American College of Medical Genetics and Genomics

CHP = UPMC Children's Hospital of Pittsburgh

CPT® = Current Procedural Terminology

ICD = International Classification of Diseases

GC = Genetic Counselor

GTC = Genetic Testing Clinic

LMN = Letter of Medical Necessity

NSGC = National Society of Genetic Counselors

UM = Utilization Management

VUS = Variant of Uncertain Significance

1.0 Introduction

1.1 Background

Genetic testing is an expanding, highly complex process that accounts for a significant portion of healthcare spending (UnitedHealth Center for Health Reform and Modernization, 2012). Currently, about 75,000 different genetic tests are available, each with their own nuances (Concert Genetics, 2018). Historically, healthcare providers specifically trained in genetics were the individuals who ordered genetic testing for their patients; however, there is a workforce shortage of trained genetics providers to offer services to all patients who could benefit from an evaluation (Billings et al., 2005; Hoskovec et al., 2018). In order to address the workforce shortage issue, as well as other barriers to accessing genetic counseling, different service delivery models have been implemented, such as telegenetics, group genetic counseling, the use of genetic counseling assistants, and other service delivery models, with varying degrees of success (Buchanan et al., 2015; Buchanan et al., 2016; Calzone et al., 2005; Cohen et al., 2012; Cohen et al., 2013; Gammon et al., 2018; Hannig et al., 2014; Hilgart et al., 2012; Kubendran et al., 2017; Ormond et al., 2018; Otten et al., 2016; Pirzadeh-Miller et al., 2017; Rothwell et al., 2012; Stoll et al., 2018). However, as genetic testing has become more commonplace, wait times for a medical genetics evaluation have increased despite the use of different service delivery models, thus an increasing number of non-genetics providers are ordering genetic testing (Dickerson et al., 2014; Kotzer et al., 2014;

Riley et al., 2015; Suarez et al., 2017). Additionally, the advent of phenotypic-driven panels have enabled non-genetics providers to choose and order genetic testing with more ease (Ingles et al., 2011; Silveira-Moriyama & Paciorkowski, 2018; Vento, 2012). To address the long wait times for a medical genetics appointment and ensure that patients are receiving quality genetics care, UPMC Children's Hospital of Pittsburgh (CHP) established the Genetic Testing Clinic (GTC) in January 2018.

The GTC is a genetic counseling-only clinic that offers same-day and advance-scheduled appointments for referrals from non-genetics providers ordering a specific genetic test. The GTC is not available, however, for medically complex patients requiring an evaluation by a medical geneticist. In circumstances where the genetic counselor (GC) identifies the need for a medical geneticist, those patients are appropriately triaged. The GTC incorporates utilization management (UM) in genetic test selection, so that the most appropriate genetic test is ordered for the patient.

Genetic testing UM has been studied by some commercial genetic testing laboratories, which identified that 8-30% of genetic tests are ordered inappropriately, such as duplicate or redundant testing or poor clinical utility based on the presenting indication (Kotzer et al., 2014; C. E. Miller et al., 2014). Furthermore, genetic UM efforts have been present in hospital systems using send out review, consultative services, and/or formulary review (Dickerson et al., 2014; Mathias et al., 2016; Riley et al., 2015; Suarez et al., 2017). However, the assessment of a program where UM GCs see patients in an outpatient setting and analyzing those pre- and post-test outcomes compared to non-genetics providers has not been performed.

The availability and depth of genetic testing is expanding rapidly, and there is a need for new genetic professional service delivery models to address this expansion. Additionally, as genetic testing becomes more routine, non-genetics providers, who may not be as familiar with

genetic information and testing nuances, are ordering genetic testing more often. The GTC aims to fill a gap between demand for genetic services, while incorporating UM and proper pre-test and post-test genetic counseling for patients. While this is a novel service delivery model, it may become more commonplace as demand for genetic services increases. This study aims to capture the benefits and possible limitations of this service, compared to genetic testing ordered by non-genetics providers alone.

1.2 Specific Aims

1.2.1 Specific Aim 1

To assess if the pre-test outcomes of genetic testing, defined as length of time for insurance authorization, appropriateness of the test order, documentation of informed consent, the extent to which family history is documented, and referrals for unrelated family history, are improved using the Genetic Testing Clinic compared to genetic testing ordered by non-genetics providers by evaluating documentation in the electronic medical record.

1.2.2 Specific Aim 2

To determine if the post-test outcomes of genetic testing, defined as genetic testing results, actionable parental testing follow-up, and medical genetics referrals, are improved using the Genetic Testing Clinic compared to genetic testing ordered by non-genetics providers by evaluating documentation in the electronic medical record.

1.2.3 Specific Aim 3

To investigate if any of the differences in post- test outcomes between the Genetic Testing Clinic and non-genetics providers can be explained by any of the demographics or pre-test outcomes by performing statistical analyses and regression modeling.

1.2.4 Specific Aim 4

To compare the percentage of genetic testing ordered with a genetic counselor's involvement compared to those ordered by non-genetics providers, from 2017 and 2018 by reviewing hospital wide data of genetic test ordering.

2.0 Literature Review

2.1 Genetic Testing and the Healthcare System

Genetic testing is an expanding, highly complex process that accounts for a significant portion of healthcare spending (UnitedHealth Center for Health Reform and Modernization, 2012). Approximately eight percent of the United States' national spending on clinical laboratory services was for genetic testing, totaling \$5 billion in 2010; this is expected to increase to \$15 to \$25 billion by 2021 (UnitedHealth Center for Health Reform and Modernization, 2012). However, the cost of genetic testing to the healthcare system is more than just the laboratory's charge, as there are doctors and genetic counselors (GCs) involved in the patient's care, potential referrals to other healthcare providers, and additional testing or screening based on the results, as well as the burden on IT to incorporate genetic testing in the EMR. Despite these costs, appropriate genetic testing can provide long-term cost savings to the healthcare system by identifying appropriate interventions for patients based on their genetic information instead of the "wait and see" or "trial and error" approach, as well as avoiding unnecessary screening and medical tests in individuals (Tammimies et al., 2015). For example, women who have a high risk for breast cancer based on personal and/or family history are recommended to have more vigilant screening, but if a *BRCA* pathogenic variant is identified, risk-reducing mastectomy and salpingo-oophorectomy is recommended, which is more cost effective than traditional radiological screening (Yamauchi et al., 2018). Similarly, if an individual with a *BRCA* pathogenic variant has a sister, but that sister tested negative for the variant, she does not have an increased risk for breast cancer and does not need increased screening, thus saving healthcare money on inappropriate screening. Appropriate

genetic testing can save money and provide better healthcare outcomes in many fields including but not limited to prenatal findings, child-onset diseases, cancer risk, and pharmaceutical dosing. As the field of genetics continues to grow and more genetic tests are offered, it is imperative to ensure proper utilization of genetic testing, both for the care of the patient as well as for the cost to the healthcare system.

2.2 Genetic Counseling

The National Society of Genetic Counselors (NSGC) defined their practice in 2006 as “the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; Education about inheritance, testing, management, prevention, resources and research; Counseling to promote informed choices and adaptation to the risk or condition” (Resta et al., 2006).

GCs are master’s level trained health care providers, receiving education in genetics, psychosocial skills, and clinical experience. Sarah Lawrence College was the first genetic counseling training program, with their first students matriculating in the Fall of 1969 (Resta, 1997). Now, there are 41 genetic counseling programs in the United States, with 404 positions available for students to enter a training program in 2018 (Accreditation Council for Genetic Counseling, n.d.; National Matching Services Inc, 2018).

Genetic counseling is a unique field that incorporates both medical and psychosocial considerations in each appointment. Typical components of a genetic counseling appointment

includes information gathering, establishing or verifying a diagnosis, risk assessment, information giving, and psychological counseling and support (Uhlmann et al., 2009). This requires a greater amount of time than a typical medical appointment and may illicit more emotion than a patient typically experiences in other medical appointments.

2.2.1 Genetic Counseling Specialties

When the field was established, GCs had limited options for specializing: either pediatric or prenatal genetic counseling, as that was reflective of the genetic tests available (Gilgenkrantz, 1977). GCs practicing in a pediatric setting typically provide genetic counseling services for families with a child with indications such as developmental delay, autism, metabolic disorder, or dysmorphic features (National Society of Genetic Counselors, n.d.) Pediatric GCs participate in the child's diagnostic odyssey by explaining genetic tests, helping families understand the diagnosis, aiding in medical referrals and support services, and providing recurrence risks (National Society of Genetic Counselors, n.d.). GCs practicing in a prenatal setting provide services for current or future pregnancies, discussing screening and diagnostic tests for chromosomal abnormalities and other genetic conditions, as well as the options of termination, adoption, donor gametes, and *in vitro* fertilization (National Society of Genetic Counselors, n.d.). Referral indications for prenatal genetic counseling can include advanced maternal age, a family history of a genetic condition, abnormal screening or ultrasounds, and exposures to teratogens (National Society of Genetic Counselors, n.d.). More recently, artificial reproductive technology and infertility genetic counseling emerged as a separate, but related specialty (National Society of Genetic Counselors, n.d.).

A third main area of specialization, cancer genetic counseling, began in the 1980s when hereditary cancer syndromes were starting to be well understood, but significantly expanded in the mid-1990s with the discovery of the *BRCA* genes (Le Marec et al., 1986; Ormiston, 1996). GCs who focus on providing cancer genetic counseling services aim to provide information to individuals and families who are at an increased risk for cancer, explain cancer screening and prevention, testing options, and how this can affect the patient's medical management (National Society of Genetic Counselors, n.d.). (National Society of Genetic Counselors, n.d.).

More recently, laboratory genetic counseling emerged as a predominant specialty in genetic counseling (National Society of Genetic Counselors, n.d.). In this service, GCs act as liaisons between the genetic testing laboratory and the ordering clinician (Christian et al., 2012; Goodenberger et al., 2015; Zetzsche et al., 2014). These counselors can help facilitate genetic testing, explain the limitations of the tests, and explain complex results.

Finally, there are additional specialties within genetic counseling - such as neurogenetics, cardiovascular genetics, ophthalmogenetics, public health genetics, research, etc. (McWalter et al., 2015; National Society of Genetic Counselors, n.d.). As genetic technologies expand and knowledge about genetic contribution to diseases grows, so does the scope of and need for genetic counseling. It is a dynamic field that continues to expand and adapt to meet the needs of the community.

2.2.2 Benefits of Genetic Counseling

GCs have a unique role in the medical field as they not only understand genetic conditions and the nuances of genetic testing, but also understand the psychosocial complexities some of these patients may be experiencing through their diagnostic odyssey, grief, or recent diagnosis. Often,

the GC can spend more time with their patients to ensure certain goals of a genetics appointment are achieved. NSGC conducts an annual professional status survey (PSS) that reported the majority (71%) of initial genetic counseling appointments last between 31 and 60 minutes, not including prep, follow up, or physician involvement (National Society of Genetic Counselors, 2018). In contrast, primary care physicians in the U.S. spend approximately 20 minutes with their patient (Irving et al., 2017). In addition to developing a close rapport with their patients, GCs also work closely with clinical geneticists and other medical specialists.

In order to measure genetic counseling outcomes in the patient setting, McAllister et al. developed a genetic counseling specific patient reported outcome measure (PROM), a 24-item genetic counseling outcome scale (GCOS-24) (McAllister et al., 2011). The study first developed an 84-item questionnaire which was completed by 527 members of patient support groups for genetic conditions in the United Kingdom. Then, the questionnaire was pared down to 24 items, based on rank order of exploratory factor analysis, psychosocial issues specific to genetic conditions, and clinical judgement on usefulness. The GCOS-24 was validated by having 395 patients attending their first genetics appointment complete the survey prior to the appointment and two to four weeks after the appointment. This test-retest analysis yielded a genetics specific PROM that is validated for analysis of construct of empowerment, shows good internal consistency, test-retest reliability, is sensitive to change, and some evidence of construct validity (McAllister et al., 2011). Since the GCOS was validated, it has been frequently used in the research process to assess outcomes and benefits to genetic counseling services.

Comparisons of patient outcomes when genetic testing is ordered with a GC compared to a non-genetics provider was performed by Cragun et al. (Cragun et al., 2015). 473 patients undergoing *BRCA* testing were surveyed to see if they recalled receiving pre-test counseling

(Cragun et al., 2015). When genetic testing was ordered with a genetic healthcare provider, patients were more likely to remember pre-test counseling occurring and recall specific aspects of pre-test counseling including: family history assessment, discussing GINA, and receiving a summary letter of the appointment (Cragun et al., 2015). Additionally, this study identified that non-genetics providers were more likely to order comprehensive *BRCA* testing when 3-site Ashkenazi Jewish testing or single site testing for a known familial variant were more appropriate (Cragun et al., 2015).

2.2.3 Workforce Shortage in Genetic Counseling

While the roles of GCs, and indications to seek a GC are expanding, there is a recognized shortage of trained GCs who can provide these needed services (Hoskovec et al., 2018). Currently, there are over 4,000 board certified GCs (American Board of Genetic Counseling, n.d.), but a workforce supply and demand model, a study of program directors, and anecdotal experiences report there is a greater demand for GCs than the number who are currently trained (Hoskovec et al., 2018; Pan et al., 2016). In 2015, the Workforce Working Group, comprised of representatives of national genetic organizations, was formed in order to quantify the workforce shortage in genetic counseling (Hoskovec et al., 2018). In combination with a workforce analysis by Dobson|DaVanzo, LLC, a model of supply of GCs and demand for services was created (Hoskovec et al., 2018). The workforce supply incorporated assumptions for the number of new genetic counseling graduates and those leaving the workforce for retirement or other reasons, while the demand was estimated at one fulltime equivalent GC working in direct patient care for 75,000 and 100,000 people (Hoskovec et al., 2018). At the time of the study in 2017, there was a shortage of 1,879 GCs in the one GC for every 75,000 people scenario or 791 in the one GC for every 100,000

people (Hoskovec et al., 2018). This report predicts an equilibrium will be achieved for supply of clinical GCs and demand for services, between 2024 and 2030 (Hoskovec et al., 2018). Some clinics are addressing the increased demands for GCs' services through a variety of unique service delivery models (Stoll et al., 2018).

2.2.4 Barriers to Genetic Counseling

While genetic counseling is a valuable resource for patients whose genetics may play a key role in their health, not all patients are referred for genetic counseling. Not only does the GC workforce shortage contribute to barriers to genetic counseling, but non-genetics providers' preparedness for the increased demand for GC services also contributed to these barriers. This was noted as early as 2005, when Billings et al. provided workshops and informational meetings about genetic services to 600 participants from a variety of healthcare roles (Billings et al., 2005). The participants included representatives from insurance companies, medical associations, and chief medical officers. They performed qualitative analysis and determined that 90% of participants had rudimentary knowledge of genetics and that 95% of participants did not have staff assigned to prepare for the influx of genomic medicine. The study also noted that the increase of genetics in medical care will warrant new service delivery models throughout medical services. While this study was published in 2005, it is worth noting that the study concluded that the medical system was not prepared for the increasing use of genomic medicine (Billings et al., 2005).

Delikurt et al. performed a systematic review of research done on barriers to genetic counseling (Delikurt et al., 2015). Of the nine articles reviewed, themes were identified on barriers due to non-genetic healthcare providers ("lack of awareness of patient risk factors, failure to obtain adequate family history, lack of knowledge of genetics and genetic conditions, lack of awareness

of genetic services, inadequate coordination of referral and lack of genetics workforce”) and the patients (“lack of awareness of personal risk, lack of knowledge and/or awareness of medical history of family members and lack of knowledge of genetic services”) (Delikurt et al., 2015). Of these studies reviewed, five were based on cancer genetics, two were based on pediatric genetics in Australia, one was based on prenatal genetics in the Netherlands, and one was based on general genetics in the U.S.; given the relevance to the present study, the general genetics study from the U.S. is reviewed below (Beene-Harris et al., 2007; Delikurt et al., 2015).

In 2007, five focus groups, consisting of a sickle cell anemia parent support group, a Native American student group, parents of children with a birth defect or other special health care needs, adults with genetic conditions, and genetics service providers, were performed to assess barriers to accessing genetic counseling services and elucidate genetics service needs in the Michigan community (Beene-Harris et al., 2007). There were 48 participants in five groups, each consisting of five to 15 individuals. The analysis of the focus group transcripts yielded topics similar to Delikurt et al, with individual barriers of lack of awareness of risk, lack of knowledge and awareness of genetic services or resources, and lack of trust and fear of discrimination identified, and institutional barriers of provider lack of knowledge and awareness of genetic services, lack of workforce, coordination of care/referral, cost and insurance, and distance from services (Beene-Harris et al., 2007).

2.2.5 Access and Service Delivery Models in Genetic Counseling

NSGC appointed a Service Delivery Model Task Force in 2009 to research various service delivery models in genetic counseling. Through discussion and informal literature review, this group defined four different types of service delivery for genetic counseling: in-person, telephone,

group, and telegenetics (Cohen et al., 2012). In-person refers to the traditional service delivery model of a face-to-face appointment between the patient and GC, while the others are newer and address certain needs in the profession and patient community. Telephone genetic counseling entails conducting the full session (not just results disclosure) over the phone; group genetic counseling is when genetic counseling is provided to a group of individuals with the same indication (such as advanced maternal age, positive prenatal screening test, or a family history of breast cancer); and telegenetics is defined as providing genetic counseling remotely through the use of videoconferencing (Cohen et al., 2012). The task force also identified five different types of referrals to genetic services: traditional, tandem, triage, rescue, and self. Traditional referrals are defined as a referral from a healthcare provider for the GC to provide all the genetic counseling and genetic test coordination. Tandem referrals entail a collaborative relationship between a healthcare provider and GC, where the healthcare provider orders the genetic testing and performs initial genetic counseling, but then refers all patients to the GC for genetic counseling and review of results. Triage referrals are similar, with the same collaborative relationship between the healthcare provider and GC, but the healthcare provider orders genetic testing and performs initial genetic counseling for routine cases, while patients with complex indications or significant family history are referred to a GC. Rescue referrals do not entail a collaborative relationship between the healthcare provider and GC; instead, they only refer to genetic counseling when there is difficulty. Self-referrals are when the patient seeks out genetic counseling themselves instead of from a provider referral (Cohen et al., 2012). Finally, the task force specified that a genetics appointment can vary based on whether or not the patient meets with the physician or has a physical examination, billing practices, and location of appointment (Cohen et al., 2012). While new service

delivery models are often defined by their mode of counseling, mode of referral and appointment logistics often yield their own unique benefits.

The task force then surveyed members of NSGC on the use of various service delivery models (Cohen et al., 2013). Of the 701 usable responses, an in-person service delivery model was used exclusively 54.7% of the time and was “always” or “often” used 95.7% of the time. 45.3 percent of respondents used multiple service delivery models. Telephone, group, or telegenetics was “always” or “often” used 13.4% of the time. Additionally, this study found through the use of multiple service delivery models, there was a decrease in patient wait time and a shorter length of appointments (Cohen et al., 2013). NSGC’s PSS identified that 59% of GCs provide direct patient care, 25% provide non-direct patient care, and 16% provide both. Additionally, of those that provide direct patient care for more than 50% of their time, 96% of GCs use in-person service delivery, 59% use telephone, 19% use telegenetics, 7% use group genetic counseling, and 65% use multiple service delivery models (National Society of Genetic Counselors, 2018).

2.2.5.1 Telegenetics

One of the first innovative service delivery models in genetic counseling was the use of telemedicine. Telemedicine is broadly defined as credentialed specialists providing remote care to medically underserved populations (Field, 1996). Applying both video and audio to clinical genetics or genetic counseling is considered telegenetics (Otten et al., 2016). The primary aim of telegenetics is to provide services to rural populations, but studies have found it to also be more cost-efficient for both patients and providers compared to in-person genetic counseling and help meet the increasing demand for genetic counseling services (Buchanan et al., 2015; Buchanan et al., 2016; Hilgart et al., 2012; Otten et al., 2016). Hilgart et al. performed a systematic review of telegenetics studies and found that all studies reported high or comparable satisfaction to in-person

appointments, and while not formally studied, telegenetics yielded cost savings to the clinic and patient, as long as telemedicine equipment was already available (Hilgart et al., 2012). A study in the Netherlands surveyed ten GCs who practiced in cancer genetics, cardiovascular genetics, and urgent prenatal genetics about their experience with telegenetics where the patients use a webcam from their home (Otten et al., 2016). This study identified that telegenetics reduces appointment time by eight percent and cost by 10 to 12%, but drawbacks of this service delivery model include insufficient non-verbal communication and technical issues (Otten et al., 2016). Buchanan et al. performed an RCT of 162 patients in rural locations to either receive in-person cancer genetic counseling at the academic medical center or video conferenced genetic counseling at a local clinic (Buchanan et al., 2015). This study identified that patient satisfaction between the two groups were similar, the telegenetics appointment cost on average \$106 compared to \$244 for in-person, but there was a higher no-show rate with telegenetics (11% for in-person compared to 21% for telegenetics) (Buchanan et al., 2015). For in-person genetic counseling, the cost for each visit was determined by the GC's travel costs, while the telegenetics cost was determined by the training time, clinical costs at the hosting site, and the telegenetics system (Buchanan et al., 2015).

2.2.5.2 Telephone Genetic Counseling

While GCs often perform intake or disclose results over the phone, full telephone genetic counseling sessions are not as common, given the opportunity of telegenetics. However, outcomes of telephone genetic counseling have been studied for both prenatal and cancer indications. Sangha et al. assessed knowledge and anxiety differences in women who received telephone genetic counseling compared to in-person genetic counseling for abnormal maternal serum screening (Sangha et al., 2003). Patients were able to select if they wanted in-person or telephone genetic counseling (an RCT failed to elicit participants), were screened for anxiety at the beginning of the

appointment, and then mailed a questionnaire eliciting anxiety and knowledge approximately two weeks after the appointment. This study had low power, with only 12 patients in each group completing the questionnaire, but both had similar knowledge scores (mean 8.3 correct answers out of 9 questions for both groups) and anxiety (mean 17.7/40 for the telephone group, mean 20/40 for the in-person group, with higher scores representing higher anxiety) (Sangha et al., 2003).

Telephone genetic counseling was also assessed by Schwartz et al. for women diagnosed with breast cancer who had a high risk of a *BRCA* mutation (M. D. Schwartz et al., 2014). In this multi-center, RCT, 335 patients had telephone genetic counseling (where a visual aid booklet was mailed to them prior to the appointment) and 334 patients had in-person genetic counseling. Genetic counseling outcomes, including knowledge, decisional conflict, cancer stress, perceived stress, general counseling satisfaction, physical function, and mental function was assessed at baseline, two weeks after genetic counseling, and three months after genetic counseling via telephone interviews using standardized questionnaires. The study found that telephone genetic counseling was noninferior in all domains (M. D. Schwartz et al., 2014). Additionally, the study performed a cost savings analysis that yielded a \$59 cost savings per patient (shared by the patient and clinic) based on no patient travel costs and decreased time in the appointment (M. D. Schwartz et al., 2014). A follow-up analysis of the same participants and interview questionnaire responses was performed by Peshkin et al. to assess patient perceptions of telephone genetic counseling (Peshkin et al., 2016). While there was no difference in satisfaction, telephone patients found the appointment more convenient, but felt less support and emotional recognition (Peshkin et al., 2016).

2.2.5.3 Group Genetic Counseling

Group genetic counseling has been implemented and studied in prenatal and cancer genetic counseling. Gammon et al. studied the use of group genetic counseling in a prenatal setting for noninvasive prenatal screening, first trimester screening, quad screening, and carrier screening (Gammon et al., 2018). The groups, consisting of two to five patients, first had the group genetic counseling session, followed by a five to ten minute individual meeting with the GC to discuss personal or family history concerns and thoughts about testing. This study used a test-retest methodology instead of comparing and found that of the 109 patients, the majority found the group session more useful than expected, patients were more prepared to make a decision regarding testing, and performed better on knowledge assessments about screening options (Gammon et al., 2018).

Rothwell et al. performed a modified patient preference study for the use of group genetic counseling for personal or family history of breast and/or ovarian cancer on cancer risk and *BRCA1* and *BRCA2* testing (Rothwell et al., 2012). This study had 32 patients who underwent individual sessions and 17 who underwent group sessions (ranging from three to five patients in each group) and determined that both groups reported high satisfaction (Rothwell et al., 2012).

While there are many benefits and positive outcomes to these different service delivery models, many of them cannot or have not been adapted to a pediatric setting. This is due to the unique nature of each patient's indication and often the need for a physical assessment by a dysmorphologist or medical geneticist.

2.2.5.4 Utilization of Genetic Counseling Assistants

A more recent intervention to improve access to genetic counseling is the incorporation of genetic counseling assistants (GCA). While there is no formal scope of responsibility for GCAs,

common duties include clerical and administrative tasks, such as data entry, ordering supplies, and administrative work, that traditionally, GCs performed, thereby allowing more time for GCs to perform job duties specific to their specialized training (Pirzadeh-Miller et al., 2017). Pirzadeh-Miller et al. performed a study at University of Texas Southwestern Medical Center (UTSW) that surveyed GCs, GCAs, and genetic counseling training program directors on experiences with GCAs and the scope of responsibilities for GCAs (Pirzadeh-Miller et al., 2017). The 22 GCs who responded to the survey stated that GCAs enabled them to have increased efficiency and time utilization (Pirzadeh-Miller et al., 2017). This study determined that GCs, GCAs, and program directors agree on the GCA responsibilities of administrative and clerical duties, however, there are conflicting responses on whether or not GCAs should call out negative or uncertain genetic testing results (all agree against calling out positive results) (Pirzadeh-Miller et al., 2017). Additionally, the study reported on their institutional patient volume as associated with the employment of GCAs. This study found that at UTSW, having a GC to GCA ratio of 3:1 yielded a 58.5% increase in new patients compared to no GCAs employed (Pirzadeh-Miller et al., 2017).

2.2.5.5 Other Service Delivery Models

GCs have developed other service delivery models to better utilize their time and improve patient outcomes by working independently, with non-genetics providers, or with different referral modalities. Kubendran et al. combined telegenetic counseling with triaging a medical genetics evaluation (Kubendran et al., 2017). Patients either had an in-person appointment with a pediatrician and a GC, an in-person appointment with the GC with a telemedicine medical geneticist, or an in-person appointment with only the GC. The pediatricians received training on genetic testing and evaluation of patients and saw patients who had nonsyndromic indications of birth defects, developmental delay, and autism, as well as evaluation for Marfan Syndrome and

Neurofibromatosis. Tele-geneticists were used in evaluation of syndromic indications, complex medical history, positive genetic tests with medical management, or negative genetic tests that warrant further investigation. Genetic counseling only was utilized for positive genetic test results that did not require a medical geneticist in ongoing management. Of the 265 patients, 149 were triaged to be evaluated first by the geneticist and 116 were triaged to the pediatrician, with 82 of those subsequently triaged onto the geneticist. 30 of the patients evaluated by the pediatrician and GC completed a survey and reported agreeing or strongly agreeing with all aspects of the genetic evaluation performed by the pediatrician, except for receiving information prior to the appointment regarding the nature of the visit. 71 of the patients evaluated by the geneticist via telegenetics completed a survey and 65% of the respondents preferred the telegenetics appointment instead of having to travel to the clinic (Kubendran et al., 2017).

Hannig et al. developed a general genetic counseling clinic under the supervision of a medical geneticist to provide genetic counseling to patients who did not require a clinical exam or have complex medical management (Hannig et al., 2014). Over two years, 321 new patients were seen for indications including family history of a genetic syndrome, personal or family history of cancer, abnormal test results, known diagnosis, and other indications or concerns. By triaging the need for a medical geneticist, the clinic reduced the patient load for the medical geneticist by 291 visits over the two years and allowed for patients to be seen in a timelier manner. Based on a survey of 30 patients seen by the GC only clinic, 77% of patients were satisfied or very satisfied with the wait time and 90% of patients were satisfied or very satisfied with aspects of knowledge of the GC and care they received (Hannig et al., 2014). Upon licensure and ability to bill for GC services, Heald et al. studied GC time involvement in GC only appointments compared to GC and MD appointments for cancer genetic counseling (Heald et al., 2013). Over eight months, six GCs saw

242 patients in the GC only appointments and 109 in the GC/MD appointments (Heald et al., 2013). The time involvement for the GC was significantly less in the GC only appointments compared to the GC/MD appointments in case preparation (16.2 vs 29.8 minutes), appointment (52.3 vs 77.0 minutes), and follow up (27.0 vs 40.3 minutes), while still performing the same amount of activities per case, indicating GC only appointments, when possible, were a better use of a GC's time (Heald et al., 2013). Similarly, CHP developed the GTC to provide genetic counseling appointments for non-genetics providers wanting to pursue genetic testing. This clinic also serves as a triage to the Medical Genetics department, for individuals with certain referrals and genetic test results that would benefit from the involvement of a medical geneticist. This novel service delivery model is the focus of this research.

The Consent and Disclosure Recommendations (CADRe) Workgroup of the Clinical Genome Resource developed rubrics on consent for genetic testing and results disclosure for nine genes based on expert consensus (Ormond et al., 2018). The rubric delineates whether there should be traditional genetic counseling, targeted discussion, or brief communication based on the indication and test results. While not yet formally studied, the goal of this intervention is to best utilize GCs, to educate non-genetics providers in genetic testing, and create a collaboration between the two, while still providing quality patient outcomes (Ormond et al., 2018).

Finally, there are other cases where GCs may not be utilized at all. This could be due to barriers to genetic counseling, non-genetics providers being comfortable with genetic testing either through additional training or experience, or other interventions that have been developed to provide appropriate genetic patient care. There are many educational aids developed by genetic testing laboratories, task forces, and medical centers that explain the genetic testing process to providers and patients. For example, Baylor College of Medicine developed Consultagene, an

online platform that provides educational materials, telegenetic counseling, peer-to-peer consultation, and interpretation of genetic testing results (Consultagene, n.d.). Another company, MyGeneCounsel, offers a subscription-based service for hospitals and patients to have up-to-date information and resources for a patient's genetic test results (My Gene Counsel, n.d.). Additionally, Geisinger Health System developed a chatbot called Genetic Information Assistant (GIA) to follow-up with participants who had American College Of Medical Genetics and Genomics (ACMG) medically actionable results from research studies (Schmidlen, 2018). GIA provides information to participants about genetics, their results, how to follow up with a provider, and how to share this with their family one month after results were disclosed by a research assistant. So far, it has been piloted by 12 participants who said it was easy and intuitive to use, but they had mixed feelings about the genetic information being delivered by the chatbot (Schmidlen, 2018).

2.3 Genetic Testing

Genetic testing can be a complicated process, with complexities in the types of testing available, interpretation of results, nuances of genotype and phenotype correlation, psychosocial considerations, management of a patient based on results, and lab and test selection. Currently, about 75,000 different genetic tests are available, each with their own nuances (Concert Genetics, 2018). The ordering provider must consider limitations of the technology, sensitivity and specificity of the test, the patient's insurance coverage, and the lab expertise. Each of these factors must be considered to offer the patient the most appropriate genetic test (if any), and how to determine appropriate follow-up based on the results of the testing.

2.3.1 Genetic Test Selection

A provider may order clinical genetic testing for a variety of reasons. Testing may be diagnostic or screening, depending on which test is used. Additionally, genetic testing can be used to determine etiology of the condition, understand how the natural history of the condition may affect the patient, assist with management and treatment, and for a patient's own understanding. The affected person can be an adult, child, or even fetus. Testing can also be performed on unaffected individuals. This may be done for reproductive planning (carrier testing), cascade testing for cancer predisposition syndromes, pre-symptomatic testing for adult onset conditions, and parental testing to assist in interpretation of a child's test result.

Genetic testing can be carried out via several different methodologies depending on the type of variant suspected. An overview of germline genetic testing methodology is outlined in **Table 1**.

Table 1. Overview of germline genetic testing methodology

Methodology	Identifiable variant	Genome analyzed	Benefits*	Limitations*
Sanger sequencing	<ul style="list-style-type: none">• Single nucleotide variants	<ul style="list-style-type: none">• Single gene• Panel	<ul style="list-style-type: none">• Accurate	<ul style="list-style-type: none">• Expensive
Next generation sequencing (NGS)	<ul style="list-style-type: none">• Single nucleotide variants• Copy number variants	<ul style="list-style-type: none">• Single gene• Panel• Exome• Genome	<ul style="list-style-type: none">• Affordable	<ul style="list-style-type: none">• Needs to be confirmed by Sanger• Promoters and introns may not be fully assessed• CNV detection is not as reliable,
Multiplex ligation-dependent probe amplification	<ul style="list-style-type: none">• Copy number variants	<ul style="list-style-type: none">• Single gene• Panel	<ul style="list-style-type: none">• Can detect small deletions and duplications	<ul style="list-style-type: none">• Expensive

Table 1 Continued

Fluorescence in situ hybridization (FISH)	<ul style="list-style-type: none"> • Copy number variants • Translocations 	<ul style="list-style-type: none"> • Certain chromosomes or regions 	<ul style="list-style-type: none"> • Detect low level mosaicism 	<ul style="list-style-type: none"> • Can miss small deletions or duplications • Does not identify break points
Karyotype	<ul style="list-style-type: none"> • Large copy number variants or aneuploidy • Translocations 	<ul style="list-style-type: none"> • Genome 	<ul style="list-style-type: none"> • Affordable 	<ul style="list-style-type: none"> • Can miss small deletions or duplications • Cannot identify regions of homozygosity
Array comparative genomic hybridization (aCGH)	<ul style="list-style-type: none"> • Copy number variants 	<ul style="list-style-type: none"> • Panel • Genome 	<ul style="list-style-type: none"> • Broad test 	<ul style="list-style-type: none"> • Can miss small deletions or duplications • Cannot identify translocations
Single nucleotide polymorphism array (SNP array)	<ul style="list-style-type: none"> • Copy number variants • Regions of homozygosity 	<ul style="list-style-type: none"> • Panel • Genome 	<ul style="list-style-type: none"> • Broad test 	<ul style="list-style-type: none"> • Can miss small deletions or duplications • Cannot identify translocations • SNP coverage dependent
Methylation analysis	<ul style="list-style-type: none"> • Aberrations in imprinting 	<ul style="list-style-type: none"> • Certain regions of chromosome 	<ul style="list-style-type: none"> • Can diagnose methylation disorders 	<ul style="list-style-type: none"> • Cannot identify any other genetic change

* Table only includes major benefits and limitations. Other benefits and limitations should also be considered in the context of the test methodology and the patient's needs.

Adapted from (Vento & Schmidt, 2012)

Similarly, genetic testing can be performed on a variety of sample types, including blood, saliva, buccal, tumor, skin biopsy, amniotic fluid, and chorionic villus sampling. Each sample type may have associated benefits and limitations that must also be considered for each patient. For example, while blood is often the best sample for germline testing, if the individual had a bone marrow transplant, a skin biopsy sample would be best because their blood will contain both the patient's DNA as well as the donor's DNA.

Once the genetic testing is agreed upon by both the patient and the ordering provider, there are many factors that need to be considered in proper lab and test selection. In *A Guide to Genetic*

Counseling, considerations for laboratory selection include genetic testing menu, specimen requirements, shipping information and kits, billing options, paperwork to accompany sample, and results (Uhlmann et al., 2009). In *Practical Genetic Counseling for the Laboratory*, other factors to consider in laboratory selection include financial considerations, technical factors, the ordering process, and customer service (McKinsey et al., 2017). In regards to financial considerations, the lab can bill the hospital, the patient's insurance, or the patient directly, and factors such as hospital contracts and discounts, CPT® coding (Current Procedural Terminology) of the tests by the lab, the patient's diagnosis(es) and corresponding ICD-10 (International Statistical Classification of Diseases and Related Health Problems) code(s), the patient's insurance, cost of reflex or cascade testing, and if free testing is available to patients that meet certain criteria may influence the cost of the genetic test (Uhlmann et al., 2009). Providers should also consider technical factors of the test including the size of the panels, the assay used to call variants, and limitations with analysis of introns, regulatory elements, or binding sites. Furthermore, labs may differ on their classification of variants of uncertain significance (VUSs) and how changes in classification would be released. Providers may also consider whether they or their patients have access to raw data, research options, and if variant data is shared with public databases. For the ordering process, provider portals, notifications for insufficient or failed samples, and turnaround time must be considered. Customer service factors include quality of the lab report and availability of a lab GC. Additionally, labs should be certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which are federal regulations for quality and safety in diagnostic testing in the United States and requires analytical validity, and accredited by the College of American Pathologists (CAP), which requires clinical validity and accuracy of diagnostic testing through a peer-based inspector model for U.S. and international labs ("Clinical laboratory improvement amendments

(42 usc 263a)," 1988; College of American Pathologists, n.d.). While this is not an exhaustive list, it contains many of the factors a provider should consider when ordering genetic testing for their patient to ensure it is the most appropriate test for the patient. CHP takes in account all of these factors in order to determine the laboratory/test formulary for genetic testing.

Due to the nuances of identifying the most appropriate test and laboratory, understanding the complexities in genetics, and providing proper informed consent, ordering genetic testing can be cumbersome. However, genetic professionals, such as medical geneticists and GCs understand these complexities and are able to incorporate these factors to provide the best patient care.

2.3.2 Genetic Test Results

For most types of genetic testing, there are three potential results: positive, negative, and VUS. The ACMG and Association for Molecular Pathology (AMP) created guidelines for classification of genetic variants into five categories: benign, likely benign, VUS, likely pathogenic, and pathogenic, based on the current body of evidence (Richards et al., 2015). A pathogenic variant (formerly known as a mutation) is considered a positive result and a likely pathogenic variant is likely a positive variant; conversely, a benign or likely benign variant is considered a negative result (Richards et al., 2015). VUSs are complex as there is not enough information for the lab to determine if the variant is pathogenic or benign; however, as more data are collected the interpretation of any variant can be reclassified (Richards et al., 2015). The issue of variant classification is complicated by the fact that different labs can have different interpretations of the same variant. After the ACMG/AMP variant interpretation criteria were published, Amendola et al. reviewed the concordance of variant interpretation across nine molecular laboratories (Amendola et al., 2016). Ninety variants were reviewed by three

laboratories while nine variants were reviewed by all laboratories; there was an initial concordance of inter-laboratory variant classification of 34%, with 22% of differences affecting medical management, which then improved to 71% after consensus discussions, with five percent of differences affecting medical management (Amendola et al., 2016).

2.3.2.1 Complexity of VUSs

Due to the way genetic variants are interpreted, VUSs are more likely to be reported in genes that are not as well studied and in ethnic minorities (Caswell-Jin et al., 2018; Haffty et al., 2009; Kessler et al., 2016; Martin et al., 2017). However, an estimated likelihood of receiving an uncertain result ranges from anecdotal reporting of one percent per gene analyzed to 7-52% in cancer panels (van Marcke et al., 2018). As more evidence is gathered, a VUS, or any other classification of variant, can be reclassified.

The majority of literature on the reclassification of VUSs is in cancer genetics. In one cancer genetics clinic, five percent (40/1103) of genetic testing reports were updated over a three-and-a-half-year time frame, but only 11% (30/266) of VUSs were reclassified; the majority of reclassifications were downgrading VUSs to likely benign (Macklin et al., 2018). Garrett et al. published about a website called FindMyVariant.org, a web-based educational resource for families with a VUS to aid reclassification through connection with other families and laboratories (Garrett et al., 2016). Tsai et al. found higher rates of VUS reclassification with increased familial testing (Tsai et al., 2018). Ninety-two patients who participated in FindMyVariant.org for over one year had an average of 4.5 relatives genotyped for the variant and yielded a VUS reclassification rate of 61% (38/62), the majority of which were downgraded to likely benign; the majority of these patients had VUSs in cancer genes (Tsai et al., 2018).

When a VUS result is received, current guidelines indicate to not use the variant to guide management, and instead to use the patient's personal and family history to guide clinical decision making (Greenblatt, 2015; Richards et al., 2015). Furthermore, providers can aid in interpretation of the variant by pursuing family studies, research studies, documenting the phenotype for the laboratory and databases, and refer to a genetics center for further aid in interpretation (Greenblatt, 2015). Additionally, there have been articles written for non-genetics providers to aid in their understanding of a patient's VUS and what it means for management and interpretation (Lindor et al., 2013; Mahon, 2015; Sijmons et al., 2013).

However, many non-genetics providers struggle with VUS interpretation (Eccles et al., 2015; Macklin et al., 2019). A survey was sent to physicians at Mayo Clinic Florida with questions regarding demographic information, comfort of genetics and VUSs, and three knowledge questions on VUSs (Macklin et al., 2019). Of the 92 respondents, only 16% answered all knowledge questions correctly and 60% were not comfortable explaining a VUS result to their patient (Macklin et al., 2019). A similar study was performed with a survey sent to breast cancer specialists in the UK with questions regarding demographic information, genetics training and comfort, and two de-identified lab reports with VUS interpretations (Eccles et al., 2015). Only 36% (56/155) of respondents were correct on VUS knowledge and skills questions; 84% of respondents correctly identified the first report as a VUS; however, the second report was correctly identified as a VUS in only 46% of the respondents and 23% interpreted the report as having no pathogenic variant (Eccles et al., 2015).

Patient knowledge of VUSs is also poor, and studies have been performed for patient understanding of VUSs in chromosomal microarrays (CMA) (Kiedrowski et al., 2016; Reiff et al., 2012) and cancer panels (Richter et al., 2013; Solomon et al., 2017; Vos et al., 2008). In Michigan,

a semi-structured phone interview was performed for 14 parents, whose child received a VUS result from a CMA 1-15 months after initial disclosure (Kiedrowski et al., 2016). Results were disclosed by a GC for nine of the patients and by a non-genetics provider from the neurology department for the remaining five patients. Although all parents could recount scientific uncertainty in the results, seven were confident the VUS was causal in the child's medical concerns, and many contradicted themselves throughout the discussion; however, no distinction of who disclosed the results was mentioned in the analysis (Kiedrowski et al., 2016). A similar study was performed by Reiff et al. where semi-structured interviews were performed for parents of children with a CMA VUS (n=14) and a CMA pathogenic result (n=11) 1-24 months after initial disclosure (Reiff et al., 2012). Results were disclosed over the phone and/or in person by either a genetics provider (GC or geneticist) or a non-genetics provider with subsequent contact by a genetics provider. Five of the parents interpreted the VUS result as causal and ten parents reported difficulty understanding the results upon initial disclosure (Reiff et al., 2012). Finally, a questionnaire was mailed to patients who underwent cancer genetic testing at a Canadian facility, regardless of test result, to gauge test result comprehension, risk perception, cancer worry, and uptake of surveillance and/or risk reduction strategies (Richter et al., 2013). Of the 144 respondents, those with VUS results had the highest observed rate of incorrectly recalled results (36%) compared to those with a pathogenic variant or no pathogenic variant identified (Richter et al., 2013).

Research has shown patient's and provider's understanding of VUSs is lacking. However, GCs understand the uncertainty in pathogenicity and are skilled at explaining this complex concept to patients.

2.3.2.2 Genetic Nuances

Even if genetic test results are clear, there are nuances of genomics that can complicate the interpretation. For example, variable expressivity and reduced penetrance can make test selection and interpretation of results more difficult, as genetic testing is not entirely predictive of the phenotypic outcomes for each patient. For example, a pathogenic variant in a cancer susceptibility gene often does not confer a 100% risk for cancer and a patient with a microdeletion might not have or develop all of the features found in other individuals with that microdeletion. Furthermore, there are technical limitations of certain testing. Besides methodological differences as mentioned previously, there can be lower coverage of certain genes or regions of genes, pseudogenes complicating testing of the desired gene, and mosaicism where platforms may vary on detection threshold. For example, even though a patient had whole exome sequencing completed, it is possible for the patient to have single nucleotide variant(s) in a gene that has a pseudogene, such as *CYP21A2* and its pseudogene, *CYP21A1*, in Nonclassic Congenital Adrenal Hyperplasia. Genetic testing can only identify variants in regions of genes with sufficient coverage, and all genetic tests have certain variants they cannot identify.

2.3.3 Psychosocial Considerations

Certain ethical principles, such as autonomy, beneficence, and confidentiality, must be considered when offering genetic testing. Completion of genetic testing can yield unique ethical, legal and social implications (ELSI). As ELSI is a well-researched topic in genetic testing, several review articles have explored these issues (Broadstock et al., 2000; Ciarleglio et al., 2003; den Heijer et al., 2013; Evers-Kiebooms et al., 2000; Green et al., 2004; Heshka et al., 2008; Hirschberg et al., 2015; Sherman et al., 2010; Willis et al., 2017).

GCs are specially trained to work with these psychosocial considerations and help families address these issues. When GCs are involved prior to genetic testing, they are able to explore the possibility of psychosocial issues that may arise upon completion of genetic testing, ensure the patient is comfortable with the genetic testing ordered, and discuss any current psychosocial concerns related to the referral.

2.3.3.1 Pediatrics

The American Society of Human Genetics (ASHG) Board of Directors and ACMG Board of Directors issued a joint statement in 1995 regarding ELSI when performing genetic testing on minors and was updated in 2015 (American Society of Human Genetics Board of & American College of Medical Genetics Board of, 1995; Botkin et al., 2015). As children cannot consent for genetic testing, their guardians must act in the best interest of the child regarding pursuit of genetic testing. The initial report suggested genetic testing can be offered for children when there are timely medical benefits related to diagnosis, prognosis, and interventions and recommended deferral of genetic testing when there is absence of timely benefit and testing for adult onset conditions (American Society of Human Genetics Board of & American College of Medical Genetics Board of, 1995). The updated report still includes these recommendations and also elaborates on nuances specific to advances in genetic testing technologies (Botkin et al., 2015). While whole genome sequencing (WGS) technology is available, the report suggests pursuing genetic testing in a stepwise manner, from single gene or small panel, to larger panel, to targeted parts of the exome or genome as it relates to the patient's phenotype; WGS is not recommended for healthy individuals (Botkin et al., 2015). Additionally, should secondary findings be elucidated, they should be actionable and disclosed to the family as decided during the informed consent or assent for adolescent (Botkin et al., 2015). The report also encourages providers and institutions

to follow other guidelines as they relate to microarray testing, newborn screening, and other genetic testing (Botkin et al., 2015).

Unique psychosocial considerations of testing children that have been studied include: how the results will be disclosed to the parents and adolescent (McGowan et al., 2018) and revealing a parent's carrier status after newborn screening (Ulph et al., 2015). McGowan et al. performed five focus groups to understand how adolescents and their parents want genetic testing results for secondary findings disclosed, and found preference for a collaborative decision-making approach of consent and assent that echoes the ASHG and ACMG report (McGowan et al., 2018). Relatedly, the results of the newborn screen and the implications for the parents can cause undue anxiety, distress, or parental guilt due to the way results are disclosed; while the anxiety and distress are often transient, greater support should be given when these results are disclosed (Ulph et al., 2015). GCs are trained on how to deliver difficult news and how to alleviate parental guilt in situations such as these.

2.3.3.2 Impacts on Life and Relationships

Once diagnosed with a genetic condition, or any chronic condition, one must adapt to that impact. One of the goals of genetic testing is to provide clarity to individuals and families on ways to improve their health or mitigate risk through behavior modifications. In a review of 30 studies, Heshka et al. found patients who tested positive for a condition that behavior change can benefit (such as increased cancer surveillance) had increased behavior modification and perceived their risk to be higher compared to patients who tested negative (Heshka et al., 2008). A different review of the literature identified that genetic disease severity does not predict adaptation, but can influence it; additionally, most individuals adapt well but there are those who do not, and children often parallel their parent's adaptation (Biesecker & Erby, 2008). Providers can aid in active

coping through assisting patients to gain control over their genetic diagnosis or by encouraging ways for the patient to express their diagnosis (Biesecker & Erby, 2008). Additionally, providers can offer education and guidance on behavior modification to better patient compliance when there is a positive genetic diagnosis (Schneider & Schmidtke, 2014). Both of these tasks are routinely performed by GCs.

Genetic testing not only has an impact on the individual, but also family members, partners, and friends. In focus groups consisting of both patients and healthcare providers, McAllister et al. sought to determine different effects the genetic diagnosis has on a family (McAllister et al., 2007). Of the seven focus groups, three had healthcare professionals, two had patient representatives, and two had patients. The patient group had two themes emerge: parent-child communication difficulties and lack of diagnosis/inappropriate care (McAllister et al., 2007). The first theme refers to the challenge parents have with talking about the diagnosis to their children, while the second theme refers to the family burden in coordinating medical care for multiple individuals with a complex genetic diagnosis. While providers did not mention these negative outcomes, they instead focused on positive outcomes of a genetic diagnosis, such as heterozygote advantage and family fit (preference to have an affected child). These differences highlight the discrepancy between experienced family outcomes and provider's perception of what those might be (McAllister et al., 2007). However, GCs are aware of the possible psychosocial implications of a genetic diagnosis and are equipped with empathetic skills to help the family cope. In a similar study, Rivard et al. performed interviews of six fathers who have a child with a genetic diagnosis (Rivard & Mastel-Smith, 2014). Using interpretive phenomenologic analysis, Rivard et al. identified themes including significant impact of diagnosis, seeking understanding, coping with the effect of the disorder, looking to the future, and addressing the father's needs. Fathers often found themselves

as advocates for their child, educating themselves, and educating the medical providers about the condition. Additionally, the fathers did not report strain on their marital relationship, but did feel like they were left out of the education compared to their wives (Rivard & Mastel-Smith, 2014). Psychosocial outcomes were also assessed for siblings of individuals with a genetic diagnosis by Fanos et al. (Fanos & Johnson, 1995). Semi-structured interviews were performed for 54 cystic fibrosis siblings and yielded differing levels of risk perception to be a carrier by birth order, resentment if the sibling passed away young, and guilt if identified to be a carrier (Fanos & Johnson, 1995). A GC's psychosocial training and counseling skills allow them to address the possible psychosocial outcome of genetic testing and how it could impact the family.

Many studies also assessed the impact on family members in a cancer genetics setting. A prospective study on family relationships in individuals who had hereditary cancer predisposition genetic testing identified that 37% had positive family interactions, such as feeling closer, improved communication and support, and relief if testing was negative; however, negative family outcomes were identified in 37% of patients, including unwanted changes in relationships, problematic situations, conflicts, secrecy, communication problems, and feelings of guilt toward those who are carriers (van Oostrom et al., 2007b). Predictors of adverse consequences include reluctance to communicate about hereditary cancer and poor family functioning (van Oostrom et al., 2007b). The study expanded and explored how family relationships can aid or harm adaptation to genetic testing results (van Oostrom et al., 2007a). Individuals who report having inhibited conversations about hereditary cancer with relatives, poor family structure, or lack of support from a partner had more cancer related stress than those who did not (van Oostrom et al., 2007a). Therefore, open communication with their family and support from a partner can be key to reducing cancer related distress (van Oostrom et al., 2007a).

Genetic testing results can have impacts on patient's and family's lives, and GCs can help them explore support and encourage behavior modification and medical referrals.

2.3.3.3 Other ELSI Considerations

The provider who orders genetic testing has certain ethical duties that must be performed. It is possible that genetic testing identifies non-paternity or that the patient's parents are close blood relatives. It is recommended to include the possibility of identifying misattributed parentage during the pre-test process (C. F. Wright et al., 2019) and poses an ethical dilemma on to whom these results should be disclosed (Tozzo et al., 2014). Furthermore, pre-test counseling should include the possibility of identifying parental relationships (Rehder et al., 2013). ACMG released a report stating that both laboratories and clinicians need to have a policy in place when regions of homozygosity are indicative of a first or a second degree relationship between the parents, especially when the mother is young or has intellectual disability, as this can be indicative of rape (Rehder et al., 2013).

Finally, upon a patient testing positive, there is a balance between the patient's autonomy to choose to share the results with at risk relatives and the provider's duty to warn at risk relatives. While court cases have yielded contradictory rulings on whether or not the provider has a duty to warn, institutions should have policies in place regarding expectations and regulations for disclosure of results to family members ("Pate v. Threlkel," 1994; "Safer v. Estate of Pack," 1996). Upon receiving consent to notify family members, a study identified a significant increase in proportion of family members receiving genetic testing (Suthers et al., 2006). Interventions, such as follow-up support upon positive testing (Gorrie et al., 2018) or direct communication with family members (Dheensa et al., 2018) may aid in dissemination of results to at risk family members. GCs assist patients once results are disclosed by writing a letter about the results and

making follow-up phone calls, both of which can increase patient understanding and familial cascade testing.

GCs are acutely aware of these possibilities and are comfortable performing appropriate follow up with the patient.

2.4 Utilization Management

The Institute of Medicine Committee on Utilization Management defines UM as “a set of techniques used by or on behalf of purchasers of health care benefits to manage health care costs by influencing patient care decision-making through case-by-case assessments of the appropriateness of care prior to its provision” (Institute of Medicine (US) Committee on Utilization Management by Third Parties, 1989). More colloquially, UM may be referred to as the right test, at the right time, for the right patient. Therefore, UM practices are not based on cost savings, rather appropriate uses of medical decision making.

Laboratory UM efforts started with routine testing, but genetic testing UM has come into light more recently. Both genetic testing laboratories and hospital systems are engaging in UM efforts by aiming to reduce errors in test selection, reduce repeat or redundant testing, increase cost savings, and improve patient impact. GCs in both clinical laboratories and hospital laboratories have a significant role in UM of genetic testing, as it both reduces medical costs while improving patient care (Kotzer et al., 2014). In addition to UM, Kotzer et al., in an opinion piece, argues that GCs in both lab and hospital settings can foster relationships with other clinicians in order to promote efficient genetic testing processes (Kotzer et al., 2014).

2.4.1 Laboratory Genetics Utilization Management

Multiple genetic testing laboratories have utilized GCs and support staff to aid in UM of tests ordered, especially for duplicate or redundant testing, reflex testing, and tests with similar names (Anderson et al., 2012; Londre et al., 2017; C. E. Miller et al., 2014; Riegert-Johnson et al., 2008; Wakefield et al., 2018). Anderson et al. reported on the role of the reference laboratory and laboratory GCs in regard to UM based on their experiences as GCs at Mayo Medical Laboratories (Anderson et al., 2012). They report three main domains in which they aid: review of appropriateness of similarly named tests, review the use of mutation screen vs known mutation test, and review for duplicate or redundant testing (Anderson et al., 2012).

Duplicate genetic testing for *HFE*, *TPMT*, and *CYP450 2D6* polymorphisms orders in 2006 was analyzed at Mayo Medical Laboratories by Riegart-Johnson et al. (Riegert-Johnson et al., 2008). The study identified 3.3% of *TPMT*, 0.9% of *CYP2D6*, and 0.3% of *HFE* orders were duplicates. While duplicate genetic testing is often not warranted, clinicians and laboratory personnel state that lack of time to review records, difficulty accessing genetic testing records, and lack of understanding that the duplicate testing will yield the same result, as reasons for duplicate testing (Riegert-Johnson et al., 2008).

UM may be viewed from a cost savings perspective instead of appropriateness of tests. Miller et al. focused on the cost savings aspect of the UM efforts of the laboratory GCs and support staff at the reference laboratory, ARUP (C. E. Miller et al., 2014). Seven GCs at ARUP reviewed molecular orders as they were received and performed pre-analytical review of the test selection and clinical information provided based on predetermined criteria for clinical utility and cost-effectiveness. If a discrepancy was identified, the GC reached out to the send out lab or ordering provider, explained the potential for improvement, and offered modification if desired. On

average, 99 genetic tests were modified each month, over 21 months. Of the modifications, 61% were misorders, such as sequencing, instead of mutation screen for carrier testing or targeted testing for a familial mutation, duplicate testing, or a test with a similar name; 34% were improvements; and five percent were other (C. E. Miller et al., 2014). The study was able to capture the benefits of UM modification as costs savings with an average savings to the payer of \$792 per misordered test, but patient care was unable to be assessed (C. E. Miller et al., 2014). While patient outcomes were not overtly assessed, Miller et al. appropriately suggests these UM interventions benefit hospitals, labs, insurers, and patients (C. E. Miller et al., 2014).

Another UM study of laboratory GCs was performed at Prevention Genetics (Londre et al., 2017). Londre et al. reports on the UM interventions performed by GCs and other laboratory staff and performed modifications in 6.6% of tests ordered over the six-month period. These modifications include reflex testing, tiered testing, the use of NGS panels instead of Sanger platforms, cancelling duplicated tests, and identifying errors in test selection due to similarly named tests (Londre et al., 2017). These interventions allowed for a cost saving to the payers of \$103,000 per month, with the biggest savings due to reflex testing and NGS testing (Londre et al., 2017).

Finally, a fourth laboratory, Molecular Genetics Laboratory at Cincinnati Children's Hospital Medical Center, reported on the use of UM for genetic testing (Wakefield et al., 2018). GCs reviewed the molecular test orders after accessioning to review appropriateness of the test(s) selected, while duplicate test review was performed by a different department and not included in this analysis (Wakefield et al., 2018). Over six months, the GCs identified 109 flagged orders, which is 4.6% of all incoming orders (Wakefield et al., 2018). Similar to other studies, common order modifications included the use of a panel instead of individual genes, reflex or tiered testing,

redundant testing, targeted testing for known familial mutations, and inappropriate testing methodologies (Wakefield et al., 2018). The GCs offered 51 test modifications, of which 49 were changed, the two not changed were due to insurance prior authorization and New York State approval, averaging \$2015.32 saved per modification, totaling to \$98,750.64 saved (Wakefield et al., 2018).

While these four genetic testing laboratories reported and assessed their UM interventions, many labs do have protocols to review proper test selection. Furthermore, it is suggested by these studies that by reaching out and educating providers, future order mistakes are prevented and a relationship with the GC is established as a resource for ordering questions (Kotzer et al., 2014; Londre et al., 2017; Wakefield et al., 2018).

2.4.2 Hospital Genetics Utilization Management

In addition to UM efforts on the laboratory side, hospitals employ UM efforts for genetic testing via send out review, consultative services, and formulary review (Dickerson et al., 2014; Mathias et al., 2016; Riley et al., 2015; Suarez et al., 2017).

At Seattle Children's Hospital, Dickerson et al. enacted a review of send-out testing meeting certain criteria: testing that costs more than \$1000, order of multiple genetic tests, sending to a non-preferred or international lab, and sending out tests that can be performed in-house (Dickerson et al., 2014). These test orders were reviewed by two pathologists, a clinical chemist, and a GC, on a rotating basis. Of the 251 cases reviewed over the eight month study period, 24% were modified upon discussion with the ordering physician, with either sequential testing (11%) or cancellation (13%), while the other 76% were approved (Dickerson et al., 2014). Through this review, \$118,952 was saved, or \$463 was saved per test reviewed (Dickerson et al., 2014). When

accounting for the salary of the test reviewers, the hospital net saved approximately \$55,000 over the eight months, making the UM review justifiable. The study also noted that 55% of genetic tests were ordered by non-genetics providers and that review of these orders often required an email or a phone call, while orders by genetics providers were often able to be reviewed with chart review alone (Dickerson et al., 2014).

The UM program at Seattle Children's was again studied by Mathias et al. after 30 months and 1,393 orders reviewed (Mathias et al., 2016). The one criterion that was modified after 27 months for UM review was a price cutoff of \$700. The UM review approved 67% of tests ordered, while 15% were changed to sequential testing, 10% were modified, and nine percent were cancelled (Mathias et al., 2016). Orders were often modified if there was an alternative test that offered improvement or better cost, while cancellation was often due to no preauthorization, deferral of testing, or wrong test selected (Mathias et al., 2016). The same proportion of tests ordered by non-genetics vs genetics providers and inpatient vs outpatient orders were approved upon UM review, but UM review yielded more cancellations for tests ordered by non-genetics providers, had more sequential tests for genetics providers, and modified more inpatient orders (Mathias et al., 2016). Additionally, of the 42 testing errors identified, the authors suggest 11 of these could have caused the diagnosis to be missed or unable to rule out the differential diagnosis. This study could only review one third of genetic test orders, due to the criteria, but notes that UM review is beneficial for cost savings and patients outcomes, even for genetic testing ordered by genetics providers (Mathias et al., 2016).

In addition to review of genetic test orders, Riley et al. at Cleveland Clinic enacted a two-part system of Clinical Decision Support Tools (CDST) and GC UM review to aid in utilization management of genetic testing orders (Riley et al., 2015). The CDST is a sort of formulary review

for 273 genetic tests that represent the highest cost to the institution. For inpatient orders, a clinical geneticist consult was required for testing that could not be deferred to the outpatient setting, and for outpatient orders, only certain providers were deemed authorized to order these tests. Riley et al. notes that this intervention actually yielded loss of potential revenue through insurance reimbursement (Riley et al., 2015). This intervention led to a genetics referral for 31% of outpatient instances and 25% of inpatient instances, while 48% of outpatient and 75% of inpatient instances did not further pursue genetic testing (Riley et al., 2015). The second intervention was GC UM review of all genetic testing ordered, including testing ordered by those authorized to do so. Over 28 months of review, 261 tests were modified, yielding a total of \$820,887 cost avoidance, or \$29,317 avoided per month. Of the tests modified, 58% were cancelled, 18% were changed to reflex testing, and 24% were modified in other ways (Riley et al., 2015). Upon review of the success of the interventions, Riley et al. suggests certain genetic tests be allowed to be ordered by genetic professionals only, similar to some drugs needing to be prescribed by certain subspecialties (Riley et al., 2015).

Finally, another genetic testing UM intervention was enacted at Stanford University Medical Center and analyzed by Suarez et al. (Suarez et al., 2017). The UM intervention was similar to Seattle Children's, with review of send out genetic testing meeting certain criteria performed by a GC, a pathologist, and a geneticist. The criteria were: tests costing more than \$2500 (eventually lowered to \$1800), concurrent genetic test orders, and sending to an international laboratory. Of the 629 genetic test orders reviewed over twelve months, 13% were classified as misorders (Suarez et al., 2017). Of the misorders, 42% were controversial orders, 29% had better alternative testing options, 17% were clerical errors, 10% were redundant testing and two percent were uncategorized misorders. An additional intervention was the availability of genetic testing

consultations provided by a GC, supported by two medical directors, at the start of the UM review intervention. The consultation included a review of the patient's medical record, evaluation of testing options, and a recommendation for a genetic test. The consultation service was utilized 71 times over the 12-month period. Additionally, misorders down trended and test modifications increased over the year, causing misordered genetic testing completed to decrease from 22% to 3% (Suarez et al., 2017). Therefore, not only did these UM interventions allow for order correction, but also impacted future order decision making through proactive consultation services, with the goal to further reduce genetic test misorders (Suarez et al., 2017).

2.5 Non-Genetics Provider's Perceptions of Genetics

While genetic testing is being ordered by non-genetics providers, research has shown that they are not as comfortable with genetics or genetic testing, and likely are not up to date with genetics knowledge, do not know how to interpret or follow-up based on results, and do not have sufficient time to go through all of the psychosocial considerations of genetic testing (Armstrong et al., 2015; Baars et al., 2005; Benseid et al., 2014; Diamonstein et al., 2018; Greendale & Pyeritz, 2001; Guttmacher et al., 2007; Harvey et al., 2007; Hofman et al., 1993; Klitzman et al., 2013; McGovern et al., 2003; Salm et al., 2014; Thurston et al., 2007).

2.5.1 Knowledge, Awareness, and Attitudes of Genetics, Genetic Counselors, and Genetic Testing by Non-Genetics Providers

Genetics can be applicable and relevant to all medical practices and patients; however, comfort, knowledge and utilization of genetics services may not be adequate in non-genetics providers. Diamonstein et al. performed a survey of non-genetics providers in Texas to assess these variables (Diamonstein et al., 2018). Of the 157 responses for practicing Texas physicians, 92% of Ob/Gyns reported genetics as moderately or very important to patient care, while 73% of pediatricians, and 24% of family and internal medicine providers felt the same, but most providers report discussing genetics more in their day-to-day practice in the past 5-10 years. Similarly, Ob/Gyns and providers in urban areas reported higher awareness of genetic services, such as referring for GC services and genetic testing. However, 72% of respondents report rarely or never referring to genetic counseling services, but are more likely to refer if they report importance to patient care. The study also surveyed perceived barriers to genetic counseling services and identified preferential referral to a geneticist instead, genetic counseling is not indicated, lack of knowing GCs to refer to, lack of knowing when a GC referral is appropriate, and not knowing how to refer to a GC (Diamonstein et al., 2018). These barriers to genetic counseling can be overcome with education resources that provide an overview of genetics and awareness of the availability of GCs.

A study performed in the Netherlands by Baars et al. identified similar results in that pediatricians and Ob/Gyns had greater genetics knowledge than general practitioners (Baars et al., 2005). A genetics knowledge survey was sent to 200 general practitioners, 300 Ob/Gyns, and 265 pediatricians in the Netherlands to build upon a previous genetics knowledge survey done by Hofman et al. in the United States in 1993 (Hofman et al., 1993). Regardless of specialty, Baars

reports that more recent graduation from medical school, genetics electives, and practicing in an urban center correlate with higher knowledge scores, emphasizing the need for continuing genetics education for practicing physicians, especially general practitioners and those in rural areas (Baars et al., 2005).

Klitzman et al. surveyed 220 internists (response rate 19.9%) at two academic medical centers to identify attitudes and practices regarding genetic testing (Klitzman et al., 2013). The survey identified that the majority (87.1%) of respondents rated their knowledge of genetic testing as somewhat or very poor, yet many (39.7%) still ordered genetic testing for their patients. Additionally, internists were more likely to order genetic testing if the patient asked about it and if patient is not African American, raising concerns about utilization of genetic testing and access to it. Despite these alarming numbers, the respondents did mention the need for further genetics training (Klitzman et al., 2013).

2.5.2 Genetics Education in Medical School

In order for primary care physicians (PCPs) and other non-genetics physicians to provide basic genetic testing and interpretation of results, there needs to be a foundation of genetics training in medical schools. The Association of Medical Colleges issued a report on genetics education in 2004, which stated competencies for education of the general physician in prevention, diagnosis, and treatment of genetic conditions, outlined concepts of attitude, knowledge, and skills related to genetics, and listed educational strategies to attain these goals (Korf, 2004). Some concepts included in the report are the need for physicians to recognize the role of genetics in health, treatment, and prevention, and the psychosocial consideration regarding genetic information,

recognizing when to refer a patient for genetic counseling, and explain and obtain informed consent (Korf, 2004).

A survey of U.S. and Canadian medical genetics course directors and curricular deans was performed by Thurston et al. in order to elucidate the genetics education in medical school (Thurston et al., 2007). Of the 75.2% of medical schools that responded, the majority (62%) report between 20 and 40 hours of genetic didactics, primarily in the first two years of medical school. Genetics instruction was described as “a broad survey of medical genetics concepts” with more than 90% of respondents including coursework on cancer genetics, mendelian genetics, and multifactorial inheritance; however, emerging genetics topics such as immunogenetics were taught in less than 50% of responding schools and few schools (11%) incorporated practical application of genetics knowledge. Thurston et al. reports that most schools teach on interpretation of genetic results and delivery of results, but was not able to assess teaching on informed consent and evaluation of genomic literature (Thurston et al., 2007).

Suggestions on improving medical school genetics training and continuing education of physicians was proposed in an opinion piece by Guttmacher in 2007 (Guttmacher et al., 2007). Guttmacher proposes that PCPs need to correctly identify patients who need further investigation or referrals to specialists, including geneticists, understand frontline genetic testing and results interpretation, and incorporate informed consent. In order to educate providers on these topics, Guttmacher suggests thorough education in medical school, including incorporation of patient care rather than lectures on broad concepts, and continuing education for providers with access to common genetics resources online (Guttmacher et al., 2007).

2.5.3 Benefits and Limitations to Genetic Testing Ordered by Non-Genetics Providers

While doctors order genetic tests in an effort to aid in the care of their patients, there can be unintended negative consequences when a non-genetics provider orders genetic testing. Benseid et al. performed a study to elucidate GCs' negative experiences when non-genetics providers order genetic testing, as such it is a biased study that sought problems with non-genetics providers ordering genetic testing (Benseid et al., 2014). They performed phone interviews with 15 GCs in Minnesota who were aware of a negative outcome from genetic testing ordered by non-genetics providers. Of the 37 specific incidents that occurred in Minnesota, 20 were related to cancer genetics, four were related to general genetics, four were related to prenatal genetics, and nine were in other specialties; 10 of these involved primary care physicians, four Ob/Gyns, three oncologists, and 14 providers from other specialties. They used inductive and case analysis methods and identified six domains: "psychosocial/emotional effects, inadequate genetic counseling, errors related to genetic tests and screening, medical mismanagement, negative attitude toward medical provider(s), and unnecessary use of health care resources" (Benseid et al., 2014). Regarding errors related to genetic tests and screening, all 13 cases had inaccurate information about interpretation of results, four had inappropriate genetic testing performed, four had incorrect genetic testing performed, and three had incomplete genetic testing (Benseid et al., 2014). Based on these descriptions of the themes and specific examples, utilization of GCs would have likely prevented these situations from occurring.

Greendale et al. discusses the benefits and limitations of utilizing PCPs for genetic services (Greendale & Pyeritz, 2001). PCPs tend to have a longitudinal relationship with their patients and this relationship can be beneficial when something as sensitive as genetic testing is ordered. One potential use of PCPs is to order genetic testing for straightforward indications. If the test is

positive, then the patient would need to be referred for proper follow up and care, but if the test is negative, the PCP would need to assess if the patient would still benefit from a thorough genetics evaluation. Additionally, the burden of knowing when to refer to medical genetics is imperative from a legal, mal-practice perspective (Greendale & Pyeritz, 2001). While this model could be beneficial, the risk of missing a referral and the fact that the model does not include comprehensive pre-test genetic counseling is a significant drawback.

Once a genetic test is ordered by a non-genetics provider, the report should be understandable by medical professionals other than geneticists and GCs. However, McGovern et al. performed a survey of NSGC members and identified that the majority of GCs have had to contact the laboratory to “obtain clarification of a report interpretation (83%), information about the methodology used (82%), interpretation of results (81%), and revised risks after negative test results (69%)” (McGovern et al., 2003). Furthermore, 28% of survey respondents indicated that genetic testing reports frequently needed to be clarified prior to disclosure to the patient. McGovern argues that if that many GCs require clarification, then PCPs and other non-genetics providers would require even more contact and clarification with the lab, or else misinterpret the genetic testing results (McGovern et al., 2003).

At CHP, the GTC was created to marry the benefits of non-genetics provider’s ordering of genetic testing with the availability of GCs to ensure proper pre-test counseling and post-test follow up. Through this service delivery model, non-genetics providers are able to assess all their patients to see if the patient would benefit from genetic testing, without having to sacrifice clinic time to review the testing process. Additionally, the UM review of the GCs creates a “safety nest” ensuring the best test for the patient is selected, without requiring the non-genetics provider to be

up to date on the latest genetics knowledge. The GTC is a novel service delivery model, and its unique benefits and limitations have not yet been assessed.

3.0 Manuscript

3.1 Background

Genetic testing accounts for a significant portion of healthcare spending in the United States (UnitedHealth Center for Health Reform and Modernization, 2012) and there are approximately 75,000 different genetic tests available on the market today (Concert Genetics, 2018). Therefore, choosing the most appropriate test for each patient is imperative, as results can be informative for treatment, management, and understanding of recurrence risk (Uhlmann et al., 2009). Many hospital institutions and genetic testing laboratories have implemented utilization management (UM) programs in order to aid proper selection of genetic testing (Anderson et al., 2012; Dickerson et al., 2014; Kotzer et al., 2014; Londre et al., 2017; Mathias et al., 2016; C. E. Miller et al., 2014; Riegert-Johnson et al., 2008; Riley et al., 2015; Suarez et al., 2017; Wakefield et al., 2018). These studies identified that UM efforts improve patient care by reducing redundant or duplicate tests, ensuring appropriateness of test, and often yield cost savings. Genetic testing UM is often supported by the work of genetic counselors (GCs).

GCs are master's educated medical professionals who discuss the role of genetics in an individual's or family's medical concerns, inform the patient of the intricacies of genetic testing, and provide psychosocial support (Resta et al., 2006). GCs render their services in a variety of healthcare settings, including pediatrics, cancer, prenatal, neurogenetics, and more (National Society of Genetic Counselors, n.d.). Benefits to genetic counseling include better patient recall knowledge and more appropriate genetic testing compared to patients who have genetic testing ordered by a non-genetics provider (Cragun et al., 2015). This is due to non-genetics providers not

being comfortable with genetics, not having up to date knowledge on genetics, and not having enough time to review all the medical and psychosocial implications of genetic testing (Armstrong et al., 2015; Baars et al., 2005; Benseid et al., 2014; Diamonstein et al., 2018; Greendale & Pyeritz, 2001; Guttmacher et al., 2007; Harvey et al., 2007; Hofman et al., 1993; Klitzman et al., 2013; McGovern et al., 2003; Salm et al., 2014; Thurston et al., 2007). However, there is a workforce shortage of GCs and medical geneticists (Hoskovec et al., 2018). While GCs and Medical Geneticists understand the nuances of genetic testing, non-genetics providers, who are often not as well versed in these details, are ordering more genetic testing as wait times for genetics appointment increase and genetic testing becomes more common (Klitzman et al., 2013).

In order to address the workforce shortage and diversifying needs of the patient communities, different service delivery models, such as telegenetics, group genetic counseling, and other unique service delivery models, have been implemented with success on providing greater access to valuable GC services (Buchanan et al., 2015; Buchanan et al., 2016; Calzone et al., 2005; Cohen et al., 2013; Gammon et al., 2018; Hannig et al., 2014; Heald et al., 2013; Hilgart et al., 2012; Kubendran et al., 2017; Ormond et al., 2018; Otten et al., 2016; Rothwell et al., 2012; Schmidlen, 2018). UPMC Children's Hospital of Pittsburgh (CHP) created an innovative genetic counseling service delivery model: the Genetic Testing Clinic (GTC).

The GTC is a genetic counseling-only clinic that offers same-day and advance-scheduled appointments for referrals from non-genetic providers within CHP ordering a genetic test. This clinic is unique in that it incorporates utilization management (UM) for the requested genetic test while providing comprehensive pre-test genetic counseling. In order to evaluate the benefits, possible limitations, and role of the GTC, the study assessed the benefits and genetic testing outcomes of this novel service delivery model one year after its inception and assessed outcomes

of genetic testing ordered by non-genetics providers prior to the creation of the GTC. The purpose of this study was to assess pre-test and post-test outcomes of genetic testing completed by non-genetics providers prior to the inception of the GTC compared to genetic testing completed through the GTC. Additionally, the study aimed to explain any differences in outcomes that are found. Finally, the study wanted to capture how genetic testing trends at CHP changed over the years.

3.2 Methods

This study was approved under Expedited Review, with a waiver of informed consent and HIPAA authorization, by the University of Pittsburgh Institutional Review Board (IRB) (PRO18060616) (Appendix A).

3.2.1 Study Population

UPMC Children's Hospital of Pittsburgh (CHP) is a nationally recognized, academic, 313 bed children's hospital in urban Western Pennsylvania.

Patients who completed genetic testing on an outpatient basis at CHP in 2017 and 2018 were included in the study. The study consists of two groups: patients who had genetic testing ordered and completed by non-genetics providers in 2017 and patients who had genetic testing ordered and completed through the Genetic Testing Clinic (GTC) in 2018. The first 150 patients who had genetic testing completed by non-genetics providers in 2017 were included in the study and GTC patients from 2018 were included until 150 had *completed* genetic testing. Thus, GTC patients who deferred genetic testing upon pre-test counseling, whose genetic testing was denied

by insurance, who did not get their sample drawn or whose insurance authorization expired, or were referred to medical genetics or neurogenetics were also assessed. Because insurance authorization can take time, some patients in the non-genetics group were seen in the year prior, yet genetic testing was drawn and completed in 2017. Additionally, non-genetics patients who were recommended genetic testing but did not complete it, due to lack of insurance approval or the patient not completing sample collection, were not included in the sample. For the purposes of this study, genetic testing is defined as germline molecular or cytogenetic testing for the purpose of diagnosis. As such, biochemical testing and tumor testing were excluded from the study. The exclusion criteria for the non-genetics providers group was the involvement of a GC or medical geneticist during the ordering process. At CHP, a GC is always involved in genetic testing in the Ophthalmology department and sometimes involved in the Neurology department. The GTC sees patients for pre-test counseling (with post-test counseling), post-test counseling only, and infants who had positive newborn screening tests (NBS) for cystic fibrosis (CF) but had negative follow-up sweat testing. As this study aims to capture the outcomes of utilizing the GTC from the start of the genetic testing process, referrals for post-test counseling only and CF NBS were excluded.

3.2.2 Data Identification

Identification of patients was completed using two methods. For the non-genetics patients in 2017, a request was sent for data on genetic laboratory testing *completed* through CHP in 2017, as all genetic testing completed at CHP must be sent out through the hospital laboratory. The report provided by the analyst was edited to include relevant genetic tests by the Genetic Counseling Supervisor of Laboratory Services at CHP, before the study PI completed data collection. There is no method available to identify when genetic testing is recommended or ordered by non-genetics

providers at CHP, unless it is actually completed. This report was also pulled for 2018 to assess the extent of a genetics provider's involvement in genetic testing.

For the GTC patients in 2018, the GCs utilize a Microsoft Access Database that is provided through a collaborative partnership with the Patient-Centered Laboratory Utilization Guidance Service (PLUGS) group, based out of Seattle Children's Hospital. A report was pulled for all the patients seen in the GTC, including post-test counseling only and CF NBS patients, which were filtered out.

3.2.3 Data Collection

The study PI used the two reports to identify patients for inclusion in the study using the inclusion and exclusion criteria and completed the retrospective electronic medical record chart review. Using the name on the report, the patient was looked up in the electronic medical record (Cerner®) at UPMC Children's Hospital of Pittsburgh and the medical record number (MRN) was saved in a separate Excel spreadsheet, according to IRB protocol. The ordering provider's corresponding note was identified, and demographic information, including age, race, sex, indication for testing, and insurance, at the time of visit was recorded by reviewing the patient information and visit history documented in the electronic medical record.

For the non-genetics patients, the clinic note was read to determine if certain aspects of pre-test counseling were discussed and documented in the note. A definition for risks, benefits, limitations, types of results, incidental findings, family history, and letter of medical necessity (LMN) language were determined prior to review of records, and the clinic note was compared against these definitions and recorded. These definitions are provided below, in **Table 2**.

Table 2. Definitions of pre-test terms

Term	Definition
Risk	Documentation of emotional consequence of genetic testing, pain of the blood draw, GINA, the word “risk”, or other risks specific to the genetic test
Benefit	Documentation of the possibility of having a diagnosis to aid in management or reproductive plans for the family, the word “benefit”, or other benefits specific to the genetic test
Limitation	Documentation of the possibility that genetic testing does not yield a diagnosis, either due to current technology or knowledge or the specific gene was not tested, or if it does yield a diagnosis there may be variable expressivity or reduced penetrance causing difficulty in prediction of specific health implications, the word “limitation”, or other limitations specific to the genetic test
Types of results	
Positive	Documentation of a specific diagnosis the genetic testing can identify, the word “positive”, or other positive results specific to the genetic test.
Negative	Documentation of the patient not having a specific diagnosis the genetic testing can identify, the word “negative”, or other negative results specific to the genetic test.
Variant of Uncertain Significance (VUS)	Documentation of genetic testing yielding a result that is not currently understood by genetics, the word “variant of uncertain significance” or “VUS”, or other variant of uncertain significance results specific to the genetic test
Incidental finding	Documentation of genetic testing being able to identify aspects unrelated to the patient’s presenting phenotype, such as non-paternity or a different genetic condition, the word “incidental finding”, or other incidental findings specific to the genetic test
Family History	
None	No documentation of any family medical concerns
Targeted	Documentation of the presence or absence of the patient’s phenotype, or related symptoms, in family members, or documentation of family medical concerns specific to that provider’s specialty
Full	Documentation of the presence or absence of the patient’s phenotype, or related symptoms, in family members, and documentation of unrelated medical concerns in third degree relatives
LMN language	Documentation for justification for the genetic testing due to aiding medical management, cost savings, practice guidelines, of other aspects of justification specific to that patient and the genetic test.

Due to the protocol of pre-test counseling in the GTC, all key elements of pre-test counseling, including: discussion of risks, benefits, limitations, the possibility of incidental findings, the possible types of results, and eliciting a full family history, are discussed and documented. The GTC utilizes clinical note templates that reflect this standardized approach. As such, for the purposes of this study all GTC patients are recorded as receiving the most comprehensive pre-test counseling possible.

Additionally, clinical utility of the genetic test and if the genetic test was most appropriate was assessed and recorded for non-genetics patients. The study PI documented the history of present illness (HPI), the genetic testing ordered, and if previous genetic testing was completed for each non-genetics patient. Two licensed and certified GCs in the GTC independently reviewed each HPI and the genetic test ordered and determined if the genetic test had clinical utility and if it was the most appropriate for that patient. If the two coders determined the same interpretation of clinical utility or if the genetic test was most appropriate, consistency was established. If responses differed, then the senior GC on the research project and Genetic Counseling Supervisor of Laboratory Services blindly reviewed the case and acted as a tie breaker.

Finally, the testing for the non-genetics patients was assessed and recorded to see if it was the preferred laboratory/test based on the CHP genetic testing formulary. The Laboratory Utilization Management team at CHP maintains a time-stamped copy of the genetic testing formulary for CHP. The 2017 genetic testing formulary list was used to assess whether the correct laboratory/test was chosen for each non-genetics patient.

Due to the GTC's protocol to have the GC thoroughly review each genetic testing referral for clinical utility, appropriateness of the genetic testing, and proper selection of laboratory, all of the GTC patients are recorded as receiving testing that had clinical utility, was appropriate, and

performed at the institution's preferred laboratory. Should the GC suggest any modifications of genetic test orders to the referring provider in order to reach clinical utility, appropriate genetic testing, or a use the institution preferred lab, documentation is performed in the EMR.

For the GTC, the clinic note was read to determine and record if there were additional benefits by having a GC. This included if there was a referral based on unrelated family history and if the GC discussed alternative genetic testing options with the referring provider. The GTC may provide unrelated family history referrals or contact information for a service different than the patient's presenting medical concerns. The GC may discuss alternative genetic testing options and the associated pros and cons of each test, based on discussion of the goals of genetic testing, family history assessment, and genetic testing formulary.

Additionally, for the GTC, the Cerner® "phone messages" note type and clinic notes from the referring provider were reviewed to determine and record if the referring provider attempted to complete the same genetic testing for which the patient was referred to the GTC.

Further chart review for both non-genetics and GTC patients included review of past laboratory testing and scanned documents to determine and record if previous genetic testing was completed. If previous genetic testing was completed, assessment was performed on the genetic test ordered to determine if there was redundant genetic testing ordered. For example, if a patient already had an epilepsy panel and then the provider ordered *POLG* sequencing, the *POLG* testing is redundant as *POLG* was already assessed on the panel. However, if a patient previously had *POLG* sequencing and then the provider ordered an epilepsy panel, the panel is not redundant, as there are other genes on the panel that were not previously assessed.

In order to determine insurance outcomes of genetic testing ordered by non-genetics providers and the GTC, clinical notes and "phone messages" were reviewed to record date of

appointment, date of submission to insurance, and date of insurance decision, as documented in the phone messages. If the phone message included an initial denial by insurance that was then approved, the date of the denial and the subsequent approval were both recorded. If the phone message documented a provider doing peer-to-peer with the insurance company, it was recorded. If the phone message included documentation of insurance requesting LMN language or a smaller genetic test, this was also recorded. If a date of insurance outcome was unknown, it was recorded as such.

For post-test outcomes, the laboratory results were reviewed to determine if the genetic testing was positive, negative, VUS, at least carrier (hereafter called carrier), or pharmacovariant, these definitions are provided in **Table 3**. The report was read to determine if the laboratory recommends parental testing and if it would be performed at no cost. If family testing was recommended, phone messages, clinic notes, and lab reports were reviewed to see if it was completed. If it was completed, review of the updated genetic testing report was completed to determine and record if parental testing reclassified a VUS.

Table 3. Definitions of results

Term	Definition
Positive	Pathogenic or likely pathogenic variant(s) that are in congruence with the inheritance pattern of the disease (ex: one single nucleotide variant identified in an autosomal dominant condition, or two single nucleotide variants identified in an autosomal recessive condition)
Negative	No pathogenic, likely pathogenic, or VUSs identified
VUS	Variant of Uncertain Significance identified in an autosomal dominant or autosomal recessive condition
At least carrier (Carrier)	Likely pathogenic or pathogenic variant in an autosomal recessive condition, no second variant identified or ruled out
Pharmacovariant	Single nucleotide variant that has implications for pharmaceutical dosing, but does not have disease manifestation

Finally, phone messages and clinic notes were read for the non-genetics and GTC patients to determine and record if there was a triage or referral to Medical Genetics (a clinic at CHP with a medical geneticist and GC) or Neurogenetics (a clinic at CHP with a medical geneticist, neurologist, and GC), which may aid in management and diagnosis of medically complex patients.

3.2.4 Data Analysis

Demographics, including age, sex, race, insurance type, and ordering department or referral department, were assessed using descriptive statistics by whether or not the genetic test was ordered through a non-genetics provider or through the GTC to understand characteristics of each sample. Types of tests ordered by non-genetics providers and referral departments to the GTC were analyzed with descriptive statistics and a two-tailed chi-square test was performed for types of tests ordered through non-genetics providers compared to the GTC to identify trends in test ordering. Exome tests were excluded from this analysis, as exomes can only be ordered through a genetics provider, based on CHP policy. Post-hoc analysis of the chi-square results was a test of proportion using two-tailed Fisher's exact comparing the proportion of each test that was ordered by non-genetics providers compared the proportion the test was ordered by the GTC, with a Bonferroni corrected p-value of 0.007.

Analysis of pre-test outcomes included a two-tailed unpaired t-test for comparison of length of time from appointment to insurance authorization submission and length of time from insurance authorization submission to approval between non-genetics and GTC patients who completed genetic testing to assess if there is a statistically significant difference in length of time between non-genetics providers and the GTC in obtaining insurance authorization. Two-tailed Fisher's exact test was used to compare if LMN language was in the note or not and if insurance

requested LMN language between non-genetics providers and the GTC to assess if there is a statically significant difference in proportion of notes having LMN language and requests by insurance for LMN language between non-genetics providers and the GTC. An unpaired t-test with Welch's correction for unequal variances was used to compare length of time for insurance authorization of non-genetics patients who had LMN language in the note compared to those that did not have LMN language. Additionally, descriptive statistics were used to asses if the patient had genetic testing previously for both the non-genetics patients and the GTC patients.

Pre-test outcomes unique to non-genetics providers were assessed with descriptive statistics and was performed for non-genetics patients, including assessing: if the test had clinical utility for the patient, if the test was the most appropriate for the patient, and if the test was performed at an institution preferred laboratory to better understand the characteristics of genetic testing as ordered by non-genetics providers. A two-tailed chi square test was performed comparing if the genetic test selected was the most appropriate for the patient or not. Post-hoc analysis of the chi-square results was a test of proportion using two-tailed Fisher's exact comparing the proportion of times each type of test selected was the most appropriate or not compared to the average rate of most appropriate test, with a Bonferroni corrected p-value of 0.01. Additionally, descriptive statistics were used to assess documentation by non-genetics providers and the GTC of risks, benefits, and limitations associated with genetic testing; the possible types of results; the extent of family history; and the possibility of incidental findings by the ordering department in order to assess documentation of informed consent and family history. Further analysis included two-tailed Fisher's exact test to compare documentation of either zero or one risk, benefit, or limitation (it did not assess differences if two or three categories of risk, benefits, or limitations were documented) and documentation zero or one possible type of result (it did not assess

differences if two or three types of possible results were documented) between neurology and endocrinology; and two-tailed chi square test was performed for documentation of no, targeted, or full family history between neurology and endocrinology to better understand differences in informed consent and documentation of family history between non-genetics departments.

Finally, pre-test outcomes unique to the GTC were assessed for all GTC patients with descriptive statistics for when the referring provider attempted insurance authorization before referral to the GTC, if a test modification was suggested, and when a referral was made by the GTC for unrelated family history to better understand the unique benefits of the GTC.

Analysis of post-test outcomes included two-tailed chi-square test of positive, negative, or VUS results between non-genetics and GTC patients to assess if there were differences in genetic testing results between non-genetics patients and GTC patients. Additionally, descriptive statistics were used for type of result by department and type of result by test for both non-genetics patients and GTC patients to assess trends in test results. Finally, two-tailed chi-square test was also performed for whether a referral to medical genetics or neurogenetics was provided between non-genetics providers and the GTC to assess if there is a difference in referral making patterns between the two service delivery models.

Regression modeling was performed to understand the interaction between demographics, pre-test variables, and post-test variables. A multiple linear regression model was used to assess whether the patient's age, sex, race, insurance type, if they have secondary insurance, if the test was ordered through non-genetics providers or the GTC, and what department was the ordering/referral department, are related to the length of time from the appointment to insurance authorization submission. Similarly, a different multiple linear regression model was used to assess whether the patient's age, sex, race, insurance type, if they have secondary insurance, if the test

was ordered through non-genetics providers or the GTC, what department was the ordering/referral department, if the provider's note included LMN language, and if insurance requested LMN language are related to the length of time from insurance authorization submission to insurance decision. A multinomial logistic regression model was used to assess whether the patient's age, sex, or race, if the patient had previous genetic testing completed, the type of genetic test ordered, if the test was the most appropriate test for the patient, if the test was ordered through non-genetics providers or the GTC, and what department was the ordering/referral department are related to the genetic test result. Similarly, a different multinomial logistic regression model was used to assess whether the patient's age, sex, or race, the type of genetic test ordered, if the test was ordered through non-genetics providers or the GTC, what department was the ordering/referral department, and the genetic test result are related to whether there is a medical genetics or neurogenetics referral.

The majority of statistical tests were completed using GraphPad Prism (v. 8, San Diego, CA) with the exception of regression modeling, which was completed with Stata (v. 15, College Station, TX). Statistical significance for all analyses was based on the conventional alpha level of significance at $p < 0.05$, unless otherwise noted.

3.3 Results

3.3.1 Patient Information

Genetic testing was completed for patients of a variety of demographics (**Table 4**). Of the 150 patients analyzed for the non-genetics group, the majority (90/150, 60%) were eight years of

age or younger at the time of consultation for genetic testing; about half (71/150, 47.33%) were male; the majority (126/150, 84%) were white; about half (84/150, 56%) had commercial insurance as their primary or only insurance; and the majority had testing ordered through neurology (77/150, 51.33%) or endocrinology (40/150, 26.67%). Of the 150 patients who completed genetic testing through the GTC, the majority (83/150, 55.33%) were eight years of age or younger at the time of consultation for genetic testing; about two-thirds were male (53/150, 64.67%); the majority (138/150, 92%) were white; about half (86/150, 57.33%) had commercial insurance as their primary or only insurance; and the majority were referred by neurology (83/150, 55.33%).

Table 4. Demographics

Demographic	Non-Genetics Number of patients (percentage)	GTC Number of patients (percentage)
Age (years)		
0-3	46 (30.67%)	45 (30%)
4-8	44 (29.33%)	38 (25.33%)
9-12	22 (14.6%)	24 (16%)
13-17	31 (20.67%)	24 (16%)
18-21	7 (4.67%)	7 (4.67%)
22+	0 (0.0%)	12 (8%)
Sex		
Male	71 (47.33%)	97 (64.67%)
Female	79 (52.67%)	53 (35.3%)
Race		
White	126 (84%)	138 (92%)
Black	14 (9.33%)	7 (4.67%)
Asian	6 (4%)	3 (2%)
Not specified	4 (2.67%)	2 (1.33%)
Insurance		

Table 4 Continued

Commercial (as primary or only)	84 (56%)	86 (57.33%)
Medicaid (as primary or only)	65 (43.33%)	64 (42.67%)
Self-pay	1 (0.67%)	0 (0.0%)
Had secondary insurance	31 (20.67%)	38 (25.33%)
Department		
Adolescent Medicine	1 (0.67%)	0 (0.0%)
Allergy and Immunology	0 (0.0%)	11 (7.33%)
Cardiology	1 (0.67%)	1 (0.67%)
Child Advocacy	2 (1.33%)	0 (0.0%)
Child Development Unit	7 (4.67%)	6 (4.0%)
Diagnostic Referral	1 (0.67%)	0 (0.0%)
Down Syndrome Clinic	1 (0.67%)	0 (0.0%)
Endocrinology	40 (26.67%)	15 (10.0%)
Gastroenterology	3 (2.0%)	9 (6.0%)
Hematology/Oncology	1 (0.67%)	7 (4.67%)
Hepatology	1 (0.67%)	2 (1.33%)
Nephrology	3 (2.0%)	5 (3.33%)
Neurology	77 (51.33%)	83 (53.33%)
Otolaryngology	8 (5.33%)	6 (4.0%)
Pulmonology	1 (0.67%)	3 (2.0%)
Rheumatology	3 (2.0%)	2 (1.33%)
Total	150 (100%)	150 (100%)

The number of diagnosis codes (ICD-10) associated with the appointment for each patient who completed genetic testing varied, with a mean of 1.46 ICD-10 codes for non-genetics patients and a mean of 1.37 ICD-10 codes for GTC patients (**Table 5**).

Table 5. ICD-10 code associated with visit

ICD-10 Code category*	Non-Genetics	GTC
Infectious Disease (A00-B99)	0	1
Neoplasms (C00-D49)	1	3
Hematologic Disorder (D50-D89)	1	6
Endocrine, Metabolic Disease (E00-E90)	15	8
Mental Disorder (F00-F99)	15	39
Nervous Disease (G00-G99)	39	32
Eye Disease (H00-H59)	2	1
Ear Disease (H60-H95)	8	5
Circulatory Disease (I00-I99)	1	1
Respiratory Disease (J00-J99)	2	3
Digestive Disease (K00-K93)	2	14
Dermatologic Disease (L00-L99)	4	1
Musculoskeletal Disease (M00-M99)	7	6
Genitourinary Disease (N00-N99)	6	5
Perinatal Condition (P00-P96)	2	0
Congenital Disorder (Q00-Q99)	13	14
Symptoms and Signs (R00-R99)	92	51
Injury and Poisoning (S00-T98)	4	0
Health Service Related (Z00-Z99)	5	15
Total	219	205

Note: Does not add to 150, due to the possibility of multiple diagnosis codes being associated with the visit

*No appointments were associated with Pregnancy, puerperium (O00-O96)

Finally, test orders were categorized into single gene, panel, exome, targeted familial sequencing, karyotype, FISH, chromosomal microarray, and Fragile X. The most common tests for non-genetics patients were panels (n=57), karyotype (n=37), single gene (n=30), chromosomal microarray (n=28), and FISH (n=23); 30 patients had two genetic tests performed at the same time. The most common tests for GTC patients were panel (n=70), chromosomal microarray (n=52),

Fragile X (n=14), and targeted familial sequencing (n=12); 13 patients had two genetic tests performed at the same time. The number of each kind of test ordered through non-genetics providers or through the GTC, with exomes excluded, was significantly different ($p<0.0001$). Post-hoc analysis test of proportion (Bonferroni corrected $p<0.007$) identified that non-genetics providers were more likely than the GTC to order single gene tests ($p=0.0007$), karyotypes ($p<0.0001$), and FISH ($p<0.0001$); non-genetics providers were less likely than the GTC to order chromosomal microarrays ($p<0.0001$), Fragile X testing ($p=0.0023$) and targeted familial sequencing ($p<0.0001$); there was no statistically significant differences between ordering panels ($p=0.253$) between non-genetics providers and the GTC. **Figure 1** outlines the types of tests ordered by department for non-genetics providers and **Figure 2** outlines the types of tests ordered by referring department for GTC.

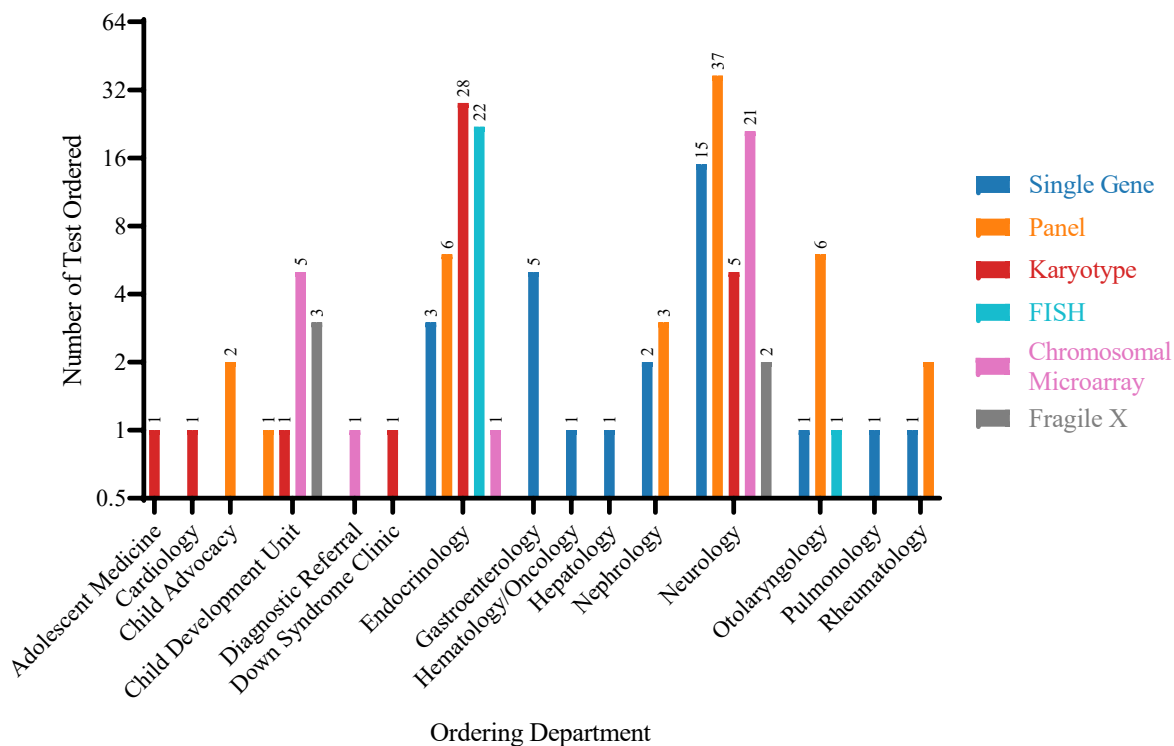


Figure 1. Genetic tests ordered by department for non-genetics providers

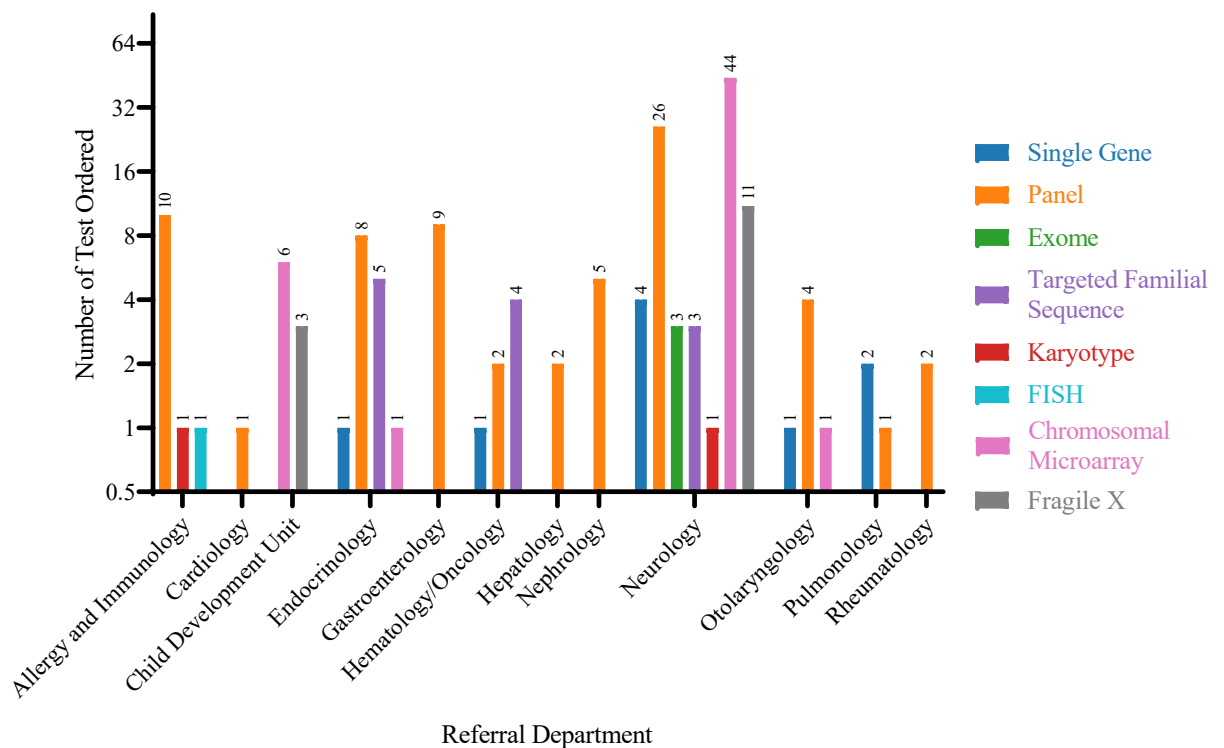


Figure 2. Genetic tests ordered by referring department for GTC

3.3.2 Pre-Test Outcomes

Of the 150 non-genetics patients' charts, 76 (51%) had documentation of submission of prior authorization to insurance and date of insurance decision. Excluding federal holidays and weekends, the mean length of time from appointment to submission for non-genetics providers was 23 days (median 13 days) and the mean length of time from submission to approval for non-genetics patients was 16 days (median 9.5 days). Of the 150 GTC patients' charts, 123 had documentation of submission of prior authorization to insurance and date of insurance decision. The mean length of time from appointment to submission for the GTC was 15 days (median 11 days) and the mean length of time from submission to approval for GTC patients was 11 days

(median 4 days). These lengths of time to submission and authorization are demonstrated in **Figure 3**. The GTC had statistically significant shorter length of time from appointment to insurance submission compared to non-genetics providers ($p=0.0068$), but the difference for length of time from submission to approval was not statistically different ($p=0.0927$).

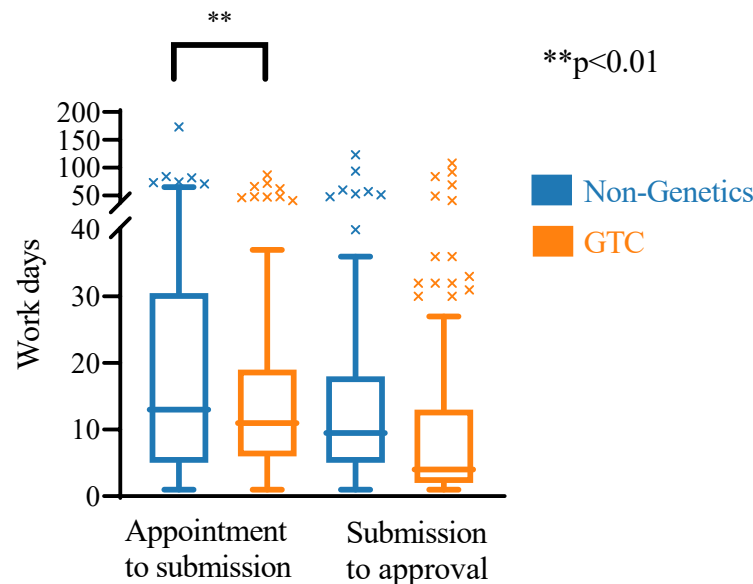


Figure 3. Box and whisker plot for length of time for submission to insurance and insurance approval

Similarly, non-genetics providers, compared to the GTC, were less likely to include language describing the medical necessity of the requested genetic test in their clinic note (20% vs 100%, $p<0.0001$) and more likely to have insurance request a letter of medical necessity (LMN) (12% vs 1.3%, $p=0.0001$). The mean length of time from submission to insurance approval for non-genetics patients without medical necessity documented in the clinic note was 18 days (median 10 days), the mean length of time from submission to approval for non-genetics patients with medical necessity documented in the clinic note was 10 days (median 6 days), and the mean length of time from submission to approval for GTC patients (who all had medical necessity documented in the clinic note) was 11 days (median 4 days). The difference in length of time for

insurance approval between non-genetics providers who did and did not include LMN language in the clinic note is significant ($p=0.03$); however, non-genetics providers that did include LMN documentation had a similar length of time for insurance approval compared to the GTC ($p=0.56$). Of the non-genetics providers, no specialty which ordered genetic testing for multiple patients routinely included medical necessity language in their note. Neurology included medical necessity language in their note 19.5% (15/77) of the time and endocrinology included medical necessity language in their note 15% (6/40) of the time. Of the referrals to the GTC, 11.2% (23/206) attempted authorization for genetic testing prior to referral.

Previous genetic testing was completed for 12.67% (19/150) of the non-genetics patients and 18.44% (38/206) of the GTC patients. There was no redundant testing when comparing current test orders with previously completed genetic testing for both non-genetics patients and GTC patients.

Clinical utility was identified in the majority of tests selected for non-genetics patients (98.67%, 148/150), while only 58.67% (88/150) were determined to be the most appropriate test for the patient based on the 2017 CHP genetic testing formulary and patient symptoms. Consistency between coders for clinical utility was 98.67% (148/150) and for the most appropriate test for the patient was 82.67% (124/150). Of the high-volume specialties, neurology selected the most appropriate test for their patient 57% of the time and endocrinology selected the most appropriate test 72.5% of the time. **Figure 4** displays the proportion of tests ordered by the non-genetics providers that were the most appropriate test for the patient, by test type. The number of times each type of test is the most appropriate for non-genetics patients, with Fragile X excluded due to small sample size, was significantly different ($p<0.0001$). Post-hoc analysis test of proportion identified that chromosomal microarray ($p=0.0025$) is more likely to be the most

appropriate test, while single gene testing ($p < 0.0001$) is less likely to be the most appropriate test. The majority of chromosomal microarrays (89%) and Fragile X (80%) orders were the most appropriate test for the patient; often, test orders of FISH (69.56%), karyotypes (67.57%), and panels (61.4%) were the most appropriate test for the patient; and rarely were single gene tests (10%) the most appropriate test for the patient. Relatedly, the GTC suggested modifications to test orders in 7.3% (15/206). Institution-preferred laboratories were utilized for all but one (99.3%, 149/150) of genetic tests selected for non-genetics patients.

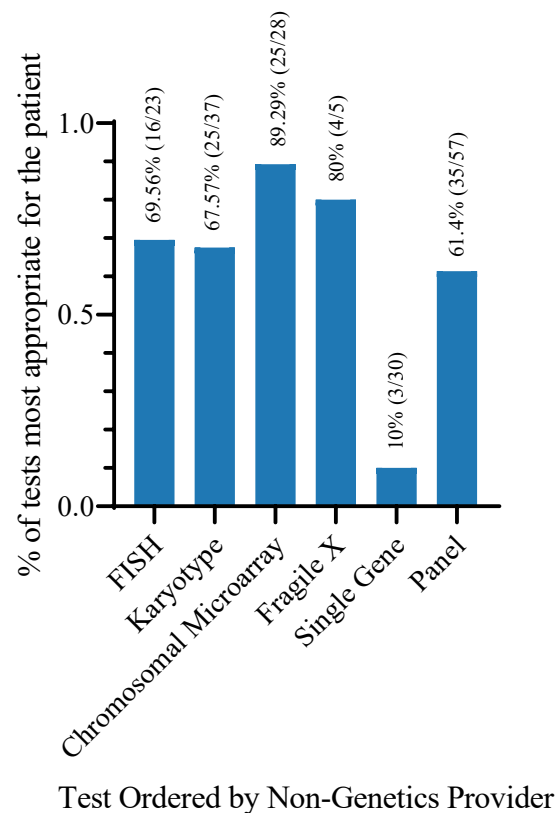


Figure 4. Proportion of tests that were the most appropriate for their patient by test selected

Pre-test counseling was categorized into documentation of discussion of risks, benefits, and limitations; the possible types of results; the possibility of incidental findings; and extent of

family history elicited. Definitions of these terms are above in **Table 2**. For documentation of discussion of risks, benefits, and limitations, the majority of non-genetics providers did not document any of these elements (74.67%, 112/150) and 23.3% (35/150) documented only one element. For documentation of the possible types of results, about half of non-genetics providers did not document any possibility (51.33%, 77/150) while the other half (44.67%, 67/150) documented one possibility. Almost none of the non-genetics providers included documentation of the possibility of incidental findings (0.67%, 1/150). Finally, the majority of non-genetics providers documented a targeted family history (56.67%, 85/150), while the remaining was almost evenly divided between no documentation of family history (20.67%, 31/150) and documentation of full family history (22.67%, 34/150). These data of pre-test counseling are presented in **Figure 5**.

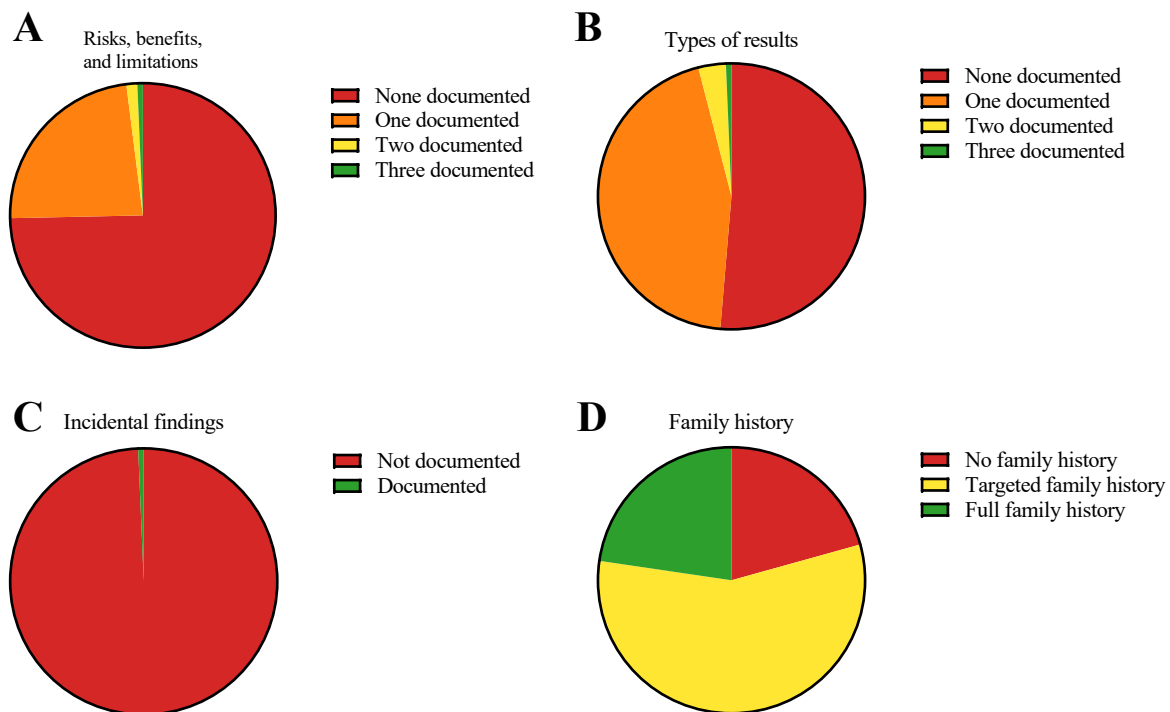


Figure 5. Documentation of pre-test counseling by non-genetics providers

A: Documentation of risks, benefits, and limitations. **B:** Documentation of types of results.
C: Documentation of incidental findings. **D:** Documentation of family history

Further analysis of pre-test counseling was completed for Neurology and Endocrinology, as they consisted of the majority of non-genetics providers test orders. The proportion of documentation of zero and one risk, benefit, or limitation between Neurology and Endocrinology providers was not statistically different ($p=0.6469$) and proportion of documentation of none, targeted, or full family history between these two departments was not statistically different ($p=0.4542$), while the proportion of documentation of zero and one types of possible results between these two departments was statistically different ($p<0.0001$).

Finally, the GTC made referrals based on family history unrelated to the patient's genetic test order 14.6% (30/206) of the time; this type of referral was made by none (0/150) of the non-genetics providers.

3.3.3 Post-Test Outcomes

Non-genetics providers had 24 positive, 23 VUSs, two carriers, one pharmacovariant, and 104 negative results. The GTC had 33 positive, 31 VUSs, two carriers, and 88 negative results. When comparing positive, negative, and VUS results, the non-genetics patients and GTC patients did not have significantly different results ($p=0.1285$). The genetic testing results are presented in **Figure 6**. Because an individual can have more than one result, the total number of results is greater than 150.

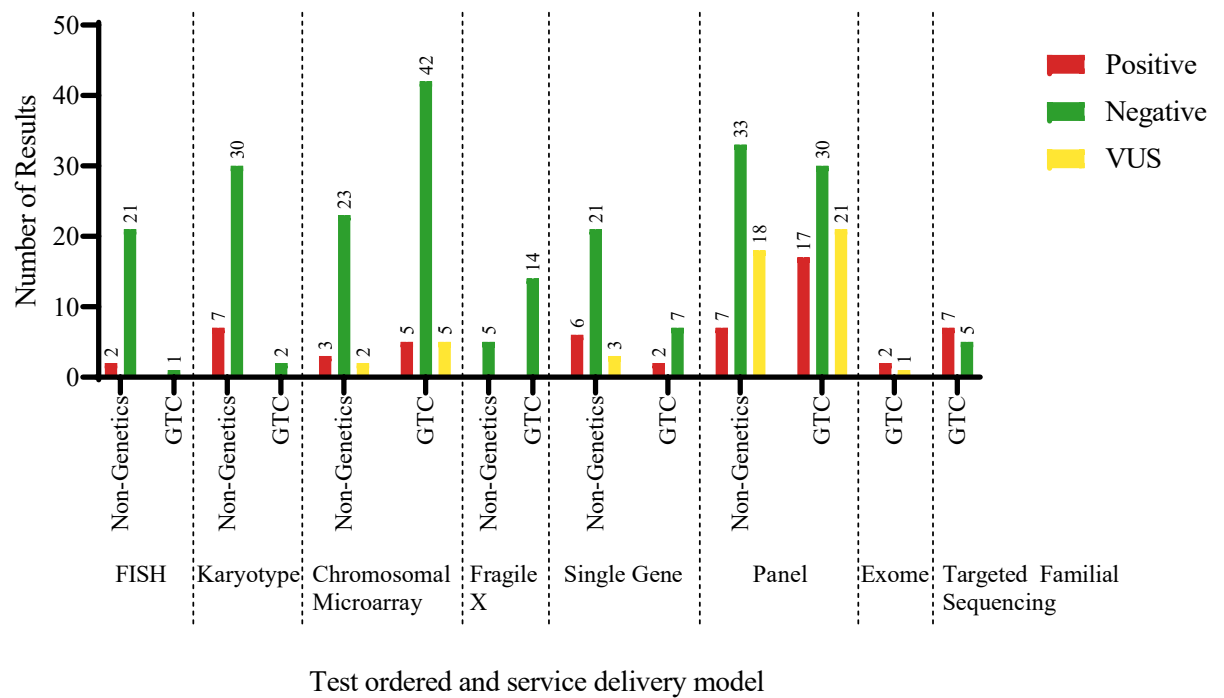


Figure 6. Genetic testing results by type of test and non-genetics or GTC

Parental VUS testing was discussed (as determined by clinic note or “phone messages” documentation), but not necessarily completed, with the family for all non-genetics patients (15/15) and all (18/18) GTC patients when the patient had a VUS warranting follow-up (either in an autosomal dominant condition, a cytogenetic change, and/or if the lab recommended free parental testing). Parental testing did not yield reclassification of the variant for any of the patients. Details of parental testing is outlined in **Table 6**

Table 6. Parental testing upon proband VUS result

Outcome	Non-Genetics	GTC
VUS in AR gene		11
VUS in AD gene or cytogenetic, or Two VUSs in an AR gene	16	20
Parental testing performed	8	8
Inherited	7	7
De novo	0	0
Not determined (one parent tested negative, other parent not tested)	1	1
Parental testing pending	0	3
Parental testing not performed	8	9
Biological parents not available	4	2
Proband lost to follow	0	3
Parent appointment issue	1	0
Parental testing not free	3	0
Parents declined testing	0	2
Parental testing not recommended by lab	0	2
Total VUSs identified	24	31

Referrals to medical genetics or neurogenetics were made upon completion of genetic testing for 21.22% (32/150) non-genetics patients and 28% (42/150) GTC patients. This difference is not statistically significant ($p=0.2279$).

3.3.4 Relationship Between Variables

Whether the non-genetics provider ordered the most appropriate test for the patient or not was not significantly associated with different test result of positive, negative, or VUS ($p=0.6996$). Furthermore, of the eight patients where test orders were modified after GC input in the GTC, one

result (1/8, 12.5%) was positive, but this gene was included on the smaller, original panel requested; two (25%) were VUSs and five (62.5%) were negative.

Multiple linear regression modeling, used to predict whether the patient's age, sex, race, insurance type, if they have secondary insurance, and if the test was ordered through non-genetics providers or the GTC are related to the length of time from the appointment to when insurance authorization is submitted. The model showed that the mean time from appointment to insurance authorization submission is 11.78 days for the GTC and is $11.78 + 8.34$ days for non-genetics providers.

In order to assess whether the patient's age, sex, race, insurance type, if they have secondary insurance, if the test was ordered through non-genetics providers or the GTC, if the provider's note included LMN language, and if insurance requested LMN language are related to the length of time from insurance authorization submission to insurance decision, a multiple linear regression model was used. The model showed that the mean time from insurance authorization submission to decision is 16.73 days, and was related to race (13.48 days longer for black patients), insurance type (10.19 days faster for patients with commercial insurance), if they have secondary insurance (8.89 days longer for patient who had secondary insurance), and if the insurance company requested an LMN (20.14 days longer if insurance requested an LMN).

A multinomial logistic regression model was used to assess whether the patient's age, sex, or race, if the patient had previous genetic testing completed, the type of genetic test ordered, if the test was the most appropriate test for the patient, and if the test was ordered through non-genetics providers or the GTC are related to the genetic test result. The model showed that microarray results are less likely to be positive and panels are more likely to have a VUS result.

In order to assess whether the patient's age, sex, or race, the type of genetic test ordered, if the test was ordered through non-genetics providers or the GTC, what department was the ordering/referral department, and the genetic test result are related to if there is a medical genetics or neurogenetics referral, a multinomial logistic regression model was used. The model showed that the referrals to medical genetics or neurogenetics is significant only for individuals who received microarray testing and negative results.

3.3.5 Genetic Testing Ordering Practices

In 2016, approximately two-thirds of genetic testing completed at CHP was ordered without a genetics professional. However, in 2018, three-quarters of genetic testing completed at CHP was ordered with a genetics professional.

3.4 Discussion

3.4.1 Pre-Test Outcomes

There were many significant benefits in pre- genetic testing outcomes when patients had genetic testing completed in the GTC compared to those completed by non-genetics providers. This is due to the unique training of GCs and the dedicated appointment time in the GTC to review the intricacies of genetic testing.

First, the types of genetic tests ordered was significantly different between non-genetics providers and the GTC, with single gene tests, karyotypes, and FISH were more commonly ordered

by non-genetics providers, chromosomal microarrays were more commonly ordered in the GTC, and panels and Fragile X testing to be ordered approximately the same amount by non-genetics providers and the GTC. Tests more often ordered by non-genetics providers are simpler and have been available for longer, compared to those ordered more often by the GTC. These simpler tests often use older technology and represent an antiquated test selection process, possibly representing non-genetics providers not being up to date in current genetic testing guidelines or methodology. This explanation is supported by Baars et al., which identified that non-genetics providers would benefit from continuing education in genetics topics, and Klitzman et al., which identified that non-genetics providers will order genetic testing, even if they report not being comfortable with their knowledge in genetics (Baars et al., 2005; Klitzman et al., 2013). However, another explanation for the simpler tests ordered by non-genetics providers could be that they ordered genetic testing for narrow indications that can be identified through these methodologies (such as wanting to prescribe Depakote and pursuing *POLG* sequencing or suspicion for Turner syndrome and pursuing a karyotype and FISH for sex chromosomes), and referred broader indications and differential diagnoses to medical genetics to pursue more complex genetic testing.

The length of time from appointment to insurance pre-authorization submission was significantly quicker for GTC patients compared to non-genetics patients. This may be explained by the dedicated insurance authorization specialists utilized by the GTC and that some non-genetics providers waited for completion of routine lab tests before pursuing genetic testing, weeks to months after the appointment. Obtaining insurance pre-authorization for genetic testing is often a complicated process, and specific workflows by CHP Genetics Department and other institutions have been implemented in order to streamline this process (Uhlmann et al., 2017). Non-genetics departments may have a sub-par system to handle the complexities of genetics pre-authorizations.

However, data for when the provider decided to pursue genetic testing was not captured and assumes it is the date of the appointment. During data collection, it was noted many times by non-genetics providers that they pursued genetic testing weeks or months after the appointment upon receipt of lab work or other clinical information, but this data was not captured or assessed, limiting the impact of this finding.

The length of time from insurance pre-authorization submission to insurance approval was not significantly different for non-genetics patients compared to GTC patients. Insurance companies often have a standard operating procedure for pre-authorization of genetic testing, explaining this consistency. However, for non-genetics patients, there was a significantly longer length of time if the insurance company requested LMN language. This is likely due to the extra time needed to notify the provider of the need of an LMN, have the provider write and submit the LMN, and the insurance company to then review the LMN. Rates of insurance authorization were not assessed as this was a study of genetic testing completed.

Non-genetics providers attempted insurance pre-authorization 11.3% (17/150) of the time before referring to the GTC to aid in obtaining pre-authorization. Some insurance companies now require genetic counseling prior to certain or all genetic testing (Cigna, 2016; UnitedHealthCare, 2015; UPMC Health Plan, 2018). The GTC can mitigate this barrier, as they offer same day appointments, thus not requiring a separate trip to the hospital to coordinate genetic testing, without which could cause a patient to become lost to follow-up. However, the study did not assess if the original genetic test order was denied due to lack of GC involvement, lack of medical necessity language, or any other factor.

It is standard practice for the GTC to include LMN language in their clinic note, while the minority of non-genetics providers included LMN language in their note. This could be due to the

genetic tests they order often do not require insurance pre-authorization (such as karyotypes), they send for insurance pre-authorization without an LMN, they submit an LMN separate from the clinic note (and not documented in the EMR) for insurance pre- authorization, or they do not understand the importance of including this information. During chart review, the latter, where the non-genetics provider mentions submitting an LMN that was not included in the EMR, was observed multiple times but was recorded as no LMN documented. Definitions of LMN vary by insurance companies, but general themes, as determined by Capasso, are clinical validity of the test, the individual is appropriate to test based on present symptoms or risk to develop symptoms, and how the genetic testing results will impact medical management and treatment of the patient (Capasso, 2014). While the former two are important, the latter is especially imperative to be documented in the EMR to allow for documentation of how the test results will impact care of the patient.

Clinical utility was identified and institution-preferred lab was used in nearly all of test selection for non-genetics patients, but about two-fifths did not have the most appropriate test selected. This could be explained by the limited clinical review performed in this study or lack of updated knowledge in genetic testing selection. For example, if a patient has intellectual disability, a karyotype does have clinical utility, but the most appropriate test for that patient would be a microarray; however, prior to microarrays, a karyotype may be the most appropriate test. Therefore, non-genetics providers have outdated knowledge or workflows related to genetic testing, they may make test selections that have some clinical utility but are not the most appropriate test. Continuing education, as suggested in the literature, can help keep non-genetics providers up to date on current testing strategies (Baars et al., 2005; Guttmacher et al., 2007). However, the proportion of tests that were most appropriate for the patient may be skewed to

appear more correct due to the insurance review process. If a non-genetics provider ordered a test that overtly is not appropriate, it is likely that insurance would decline that inappropriate test. Previous studies have improved or modified genetic test selection in 5-32% of laboratory-initiated processes and 13-25% of institution-initiated processes (Dickerson et al., 2014; Londre et al., 2017; Mathias et al., 2016; C. E. Miller et al., 2014; Suarez et al., 2017; Wakefield et al., 2018). The 41.33% of genetic tests that were not the most appropriate for non-genetics patients is higher than what the literature reports. While these test orders were not modified due to the retrospective methodology of this study, the higher rate of possible test modification could represent more genetic test education needed by non-genetics providers at CHP, more stringent UM review by the GTC compared to other studies, or the rate could be similar to previous studies if non-genetics providers were given the opportunity to cancel testing upon UM review. Relatedly, the GTC suggested UM modifications to test orders in 5.33% of patients. This finding is lower than what other institution-initiated genetic UM review processes report. This may be reflective of recent educational grand rounds about genetic testing that may have improved knowledge between 2017 and 2018, the possibility that non-genetics providers at CHP who know about the GTC make better genetic test selections, the UM review at the GTC was performed for *all* tests ordered through this particular service delivery model, while other programs in the literature perform UM review of genetic testing ordered through a specific service delivery model, have a monetary cutoff, or other criteria, the majority of genetic tests ordered for the GTC were chromosomal microarrays which is a first tier test and often the most appropriate, or because the GTC triaged medically complex patients to Medical Genetics clinic where more UM test selection was not reviewed. Finally, while previous genetic testing was completed for some non-genetic and GTC patients, none had redundant testing. Redundant testing differs from duplicate testing, in redundant testing is

repeating a small part of a test that has already been performed, but may be called something different (such as a chromosomal microarray and a FISH, or a panel and a single gene that is included on the panel). Duplicate testing is often assessed in UM review, and 0% duplicate testing, in addition to 0% redundant testing, is better than the 1-3% of duplicate testing and 10% redundant testing reported in the literature (Riegert-Johnson et al., 2008; Suarez et al., 2017).

Documentation of pre-test counseling and assessment done by non-genetics providers is worse than what is typically done in appointments by GCs in the GTC. For risks, benefits, and limitations, almost all of non-genetics providers only documented one aspect (23.3%) or did not document any (74.67%) risks, benefits, or limitations. Similarly, almost all non-genetics providers documented only one possible type of result (44.67%) or did not document any possible types of results (51.33%). Finally, almost none (0.67%) of the non-genetics providers documented the possibility of incidental findings. Documentation of the possibility of secondary findings was not assessed, as secondary findings are most often associated with whole exome or genome sequencing, which is only available at CHP through subspecialty clinics such as Medical Genetics or Neurogenetics. While there is no literature assessing pre-test counseling performed by non-genetics providers or the extent of medical school education on pre-test counseling (Thurston et al., 2007), there are practice guidelines that support non-genetics providers ordering appropriate genetic testing and recommend communicating the risks, benefits, and limitations of the test and the possible types of results to the patient (Satya-Murti et al., 2013). These guidelines also mention that if the non-genetics provider does not have enough knowledge or comfort with genetics, they should refer to a GC or other qualified health care provider to counsel the genetic test offering (Satya-Murti et al., 2013).

Regarding documentation of family history, non-genetics providers often (56.67%) had a targeted family history and some (22.67%) had documentation of full family history; about one-fifth (20.67%) did not have any documentation of family history. Many organizations support the provider taking a comprehensive, three generation family history (American College of Obstetricians and Gynecologists Committee on Genetics, 2011; American Medical Association, 2004; Rich et al., 2004; Wattendorf & Hadley, 2005); however, the majority of providers in this study only documented a targeted family history. There is no literature supporting a limited family history over a full family history; however, non-genetics providers tend to opt for limited family history relevant to the patient's chief complaint. This could be due the increased amount of time required to take a comprehensive family history and lack of education or training on the benefits to taking a full family history, Thorough family history assessment that could identify other risk factors, as represented by the 14.6% of patients in the GTC who received referrals for unrelated family history. To aid appropriate referrals upon comprehensive family history assessment, ACMG and NSGC developed guidelines for non-genetics providers on when to refer to a GC (Hampel et al., 2015; Pletcher et al., 2007).

Finally, further analysis of documented pre-test counseling was performed between Neurology and Endocrinology. There were no significant differences in documentation of risks, benefits, and limitations, or documentation of family history, however there was a significant difference of documenting zero or one type of possible results, with endocrinology more likely to document one type of possible result. This is likely due to endocrinology often ordering karyotypes for limited indications, such as Turner Syndrome or Klinefelter Syndrome, which counted as documentation of one type of result, and neurology ordered panels or microarrays for broader indications such as epilepsy or autism, where a specific differential diagnosis is not suspected.

Upon completion of comprehensive family history assessment, GCs in the GTC made a referral for unrelated family history for 14.6% of patients. This is similar to the 21% (88/416) of prenatal genetic counseling patients that GCs identified an adult or cancer GC referral (McClatchey et al., 2018), as comprehensive family history assessment is a core duty of a GC (Resta et al., 2006). By making appropriate referrals, families understand how genetics plays a role not only in their child's primary indication for genetic testing, but also how genetics can explain a family history of cancer or cardiac involvement. These referrals can identify families at high risk for certain health implications and may have a pathogenic variant in one of the ACMG 59 genes, which are present in approximately 1-3% of the healthy population (Haffty et al., 2009; Olfson et al., 2015).

This study highlights the benefits of the GTC, including thorough pre-test counseling, comprehensive family history assessment, and UM review. By increasing access to quality genetics care, the GTC improves patient care by ensuring proper informed consent, providing appropriate follow-up, and completing the most appropriate genetic testing. A similar service delivery model that combined consultative services and UM review has shown great success on improving provider ordering practices (Suarez et al., 2017).

3.4.2 Post-Test Outcomes

There were no significant differences in the post-genetic testing outcomes assessed in this study between patients who had genetic testing completed through a non-genetics provider and the GTC. However, the GTC does offer post-test counseling, which is a valuable resource to aid in understanding of genetic testing already completed.

Genetic testing results were statistically similar between the two groups. While it might be expected that there is a higher diagnostic yield using the UM GTC clinic, this could be explained by both groups of patients not being as medically complex and the varying diagnostic yield of genetic testing technology. Literature reports the diagnostic yield of a chromosomal microarray, when used as a first tier test for individuals with developmental disabilities or congenital anomalies, to be 15-20% (D. T. Miller et al., 2010), however, the diagnostic yield of the microarray for non-genetics and GTC patients was 10.7% and 9.6%, respectively. The diagnostic yield in both clinics being lower than reported could be due to patients not being as medically complex as Medical Genetics patients.

Uptake of parental VUS testing was also statistically similar between non-genetics patients and GTC patients. While there is no literature on follow up parental testing when recommended for VUS resolution in a proband, it was reassuring that the non-genetics patients had similar outcomes to the GTC patients. However, both groups of patients had biological parents that were not available and patients that were lost to follow up, phenomena that are reasonable and within normal limits, decreasing the uptake of parental VUS testing. For the GTC, 9.7% of VUS patients were lost to follow-up. Conversely, 16% of non-genetics patients and 6.4% of GTC patients with VUSs did not have biological parents available. Of note, laboratories did not recommend parental VUS testing for two non-genetics patients and two GTC patients who had a VUS in an autosomal dominant gene or in cytogenetic region. For the GTC patients, both also had a pathogenic variant that was explanatory for the phenotype.

Finally, referral rates to Medical Genetics and Neurogenetics were statistically similar. This is expected, given the study design to look at comparable populations and the statistically similar genetic test results between the two groups. By referring to Medical Genetics or

Neurogenetics, the provider allows the patient to receive a more comprehensive evaluation and management of care.

3.4.3 Relationship Between Variables

Genetic testing results for non-genetics patients who did have the most appropriate genetic test did not significantly differ from those who did not have the most appropriate genetic test. There are several possible explanations for this result. First, because this is an assessment of genetic testing completed, insurance likely denied genetic test selection that had no utility or was grossly inappropriate. Additionally, appropriateness was determined by UM GCs, who take in account cost effectiveness and contract pricing with laboratories, meaning that the most appropriate test could be a similar panel that offered more genes. Finally, the additional genes on broader panels likely represent a minority of diagnoses compared to the original genes on smaller panels. Therefore, a minor increase in diagnostic yield would be expected with broader panels, but may not have been appreciated in this small sample size.

While the GTC did offer test modification to 14.6% of patients, only eight of them completed genetic testing, and only one of those were positive. Therefore, increased diagnostic yield due to UM modification cannot be assessed due to the small sample size; however, UM modification can yield cost savings, though this was not studied.

No demographic factors were found to be associated with length of time from appointment to insurance authorization in regression modeling, as the only significant result was non-genetics providers taking about 8 more days to submit for insurance authorization, as previously identified in pre-test outcome assessment.

Regression modeling to predict length of time from insurance authorization submission to approval did yield informative results. First, approval took approximately 13 days longer for black patients. This difference is unexpected and could reflect disparities in healthcare or could be due to the groups being inherently different. Second, insurance approval was about 10 days faster for patients with commercial insurance. This could be due to commercial insurance companies having more resources for authorization processes compared to government issued insurances. Third, approval for patients with secondary insurance was about nine days longer than those without it. Due to the way data were captured as the length of time from insurance authorization submission to approval was defined as length of time from initial insurance authorization submission to final approval. Therefore, if the patient's primary insurance denied the genetic test, and the provider then submitted to secondary insurance that approved the genetic testing, the back-and-forth between insurance companies was included in the time assessment. Finally, approval took about 20 days longer if the insurance company requested an LMN. Again, this is likely reflective of the back-and-forth interactions between the provider and the insurance company. This highlights the importance of including LMN language in the clinic note, which the GTC always does.

Regression modeling to predict genetic testing result provided significant results consistent with the literature. First, chromosomal microarray testing is less likely to yield a positive result. It is a first-tier test for individuals with developmental delay or multiple congenital anomalies, due to the cost-effective nature of its diagnostic yield, with a diagnosis being identified approximately 10-20% of the time. This diagnostic yield in the literature is similar to the 10.1% (8/79) in this study (Rehder et al., 2013; Tammimies et al., 2015). Second, multigene panels are more likely to yield a VUS. Given that VUS rates for panels range from one percent per gene analyzed to 7-52% in cancer panels (van Marcke et al., 2018), a high likelihood for a VUS result is expected and

consistent with what was identified in this study. Finally, an increase in patient age is less likely to have a positive genetic testing result.

The last regression model was performed to predict referrals to Medical Genetics or Neurogenetics. It was significant for chromosomal microarray more likely to receive a referral and negative results less likely to receive a referral. Patients who have developmental delay or multiple congenital anomalies should not only have chromosomal microarray as the first-tier test, they also should receive a thorough evaluation by a geneticist/dysmorphologist as they can suggest further testing if the microarray is negative or guide management if the microarray is positive. Patients who receive a negative test result were less likely to receive a referral for a genetics evaluation. While a geneticist might offer further testing for these patients, many providers ordered genetic testing to rule out a specific genetic condition, with plans to continue to care for the patient based on their presenting features and symptoms; however, an evaluation by a medical geneticist could still be beneficial in care management.

3.4.4 Case Example Vignettes

Many times, the most appropriate test was not selected by the non-genetics provider, both when ordering in 2017 and when referring to the GTC in 2018. While test modification was not possible for non-genetics providers' orders in 2017 due to the retrospective chart review nature of this study, alternative testing strategies were discussed upon data collection.

3.4.4.1 Non-Genetics Providers

An endocrinologist wanted to test for Prader-Willi Syndrome (PWS). The provider ordered a PWS FISH test which was negative; however, FISH will only identify about 65% of patients

with PWS. Instead, an MS-MLPA test that assesses for methylation aberrations will be able to identify 99% of cases, making it a more appropriate test to order.

A neurologist wanted to provide genetic testing for an infant with epilepsy. The family history was also significant for infantile epilepsy. While the provider did order an infantile epilepsy panel, GC UM review suggests that a more comprehensive epilepsy panel would be more appropriate. This is because genes on the more comprehensive panel can still present in infancy and if the infantile epilepsy panel was negative, it would be difficult to get a more comprehensive test approved later.

A nephrologist evaluated a patient where Focal Segmental Glomerulosclerosis (FSGS) was on the differential, so the provider ordered a FSGS panel; however, the provider also wanted to assess *APOL1*, which was not included on the panel, so they ordered a single gene test in addition to the panel. A more cost-effective choice would be to identify a panel that included all the genes the provider wanted to assess or create a panel if one does not exist.

Finally, a neurologist evaluated a male who has autism, developmental delay, staring spells, and large ears. The provider ordered a karyotype, which was negative; however, a chromosomal microarray is the first tier test for individuals with autism (D. T. Miller et al., 2010). Additionally, at CHP, Fragile X is often ordered in conjunction with chromosomal microarrays when the indication is Autism or developmental delay.

3.4.4.2 GTC

A patient with photogenic epilepsy, autistic features, and developmental delay, and had a normal oligoarray was referred to the GTC. The referring neurologist selected a comprehensive epilepsy panel (127 genes); however, an expanded epilepsy panel (1300) genes was suggested by the UM GCs as this test offers a broader scope at a similar price.

Otolaryngology referred a patient with bilateral sensorineural hearing, with a family history significant for hearing loss. The provider suspected Pendred Syndrome and selected a Pendred Syndrome panel. However, given that the family history does not reflect the autosomal recessive pattern of inheritance consistent with Pendred Syndrome, the UM GC suggested a broader hearing loss panel that could identify more diagnoses with a broader range of presentations.

A patient was referred by neurology for a SNP microarray, PWS methylation, and Fragile X. Given that a SNP microarray can detect about 70% of PWS as well as many other diagnoses, the provider agreed with the UM GCs suggestion to pursue a SNP microarray and Fragile X, then refer to Medical Genetics upon a negative result.

Finally, the UM GCs partnered with Gastroenterology providers to develop a custom pancreatitis panel that included all the desired genes at a reasonable contracted price with the lab. By doing this, they created the most appropriate test, based on utility of genes and cost, instead of having to pursue subpar panels or sequential testing that could increase cost and delay diagnosis.

Through UM review, the GTC model allows for the most appropriate genetic test to be ordered for each patient. The UM formulary at CHP accounts for cost-effectiveness and clinical utility of the test. Therefore, healthcare dollars are spent more appropriately and patients are receiving the most relevant genetic testing due to the GTC's UM review.

3.4.5 Study Limitations

While this study has assessed the benefits of a novel genetic counseling service delivery model not characterized in the literature, it is limited by the retrospective chart review methodology. The analysis heavily relies on assessment of what is documented in the patient's EMR; however, EMR templates can include documentation of events that did not occur with the

patient or conversely, everything that did occur with the patient may not have been documented in the EMR. This limitation was especially noticed when assessing the length of time from appointment to submission of insurance pre-authorization, and from submission to authorization, as this was only documented in about half of non-genetics patient's charts. However, there are likely other aspects of this study not documented or documented erroneously, such as discussion of informed consent. Problems and errors with EMR documentation and the use of templates is not unique to CHP, as it has been studied numerous times in the literature and can cause liability issues (Bowman, 2013; Zahabi et al., 2015).

Similarly, this study had to simplify the definitions of informed consent, documentation of family history, and LMN language. For aspects of informed consent and LMN language, very specific language had to be documented in the clinic note to count as documentation; however, it is possible these variables were documented without that phrasing. For family history, the definition of a full family history specific did not include “a three-generation pedigree”, as GCs tend to be the only providers that utilize this methodology. Instead, the definition “documentation of the presence or absence of the patient's phenotype, or related symptoms, in family members, and documentation of unrelated medical concerns in third degree relatives” was used. This definition would count a patient with Autism as an indication, with documented family history of a grandparent with hearing loss as a full family history, when other family history aspects, such as cancer, were possibly not fully assessed and documented.

Additionally, this study assessed genetic testing outcomes in patients that *completed* genetic testing. Further assessment of those where genetic testing was ordered, but not completed due to insurance denial, change of mind, etc. would be beneficial to the literature to understand differences between patients who do not complete genetic testing when it is ordered and those who

do. It would also be helpful to better understand if there are any pre-test outcomes or differences between non-genetics providers and the GTC that can explain these differences. It is possible for there to be higher rates of insurance denial in non-genetics providers compared to the GTC due to inappropriate test selection, and this in addition to rates of patients choosing to move forward with genetic testing would be interesting to study.

Further, this study focused on genetic testing completed for non-genetics patients in 2017 and GTC patients in 2018. This was due to the assumption that non-genetic providers can refer to the GTC in 2018, so the population of patients who receive genetic testing would be comparable. However, patients who had genetic testing completed through non-genetics providers in 2018 were not assessed. Perhaps they were not referred to the GTC due to the routine nature of genetic testing, the provider's familiarity with genetic testing, or the provider was unaware of the GTC. However, further assessment of genetic testing not completed through the GTC (or with the aid of a genetics provider) could identify if there are gaps in the GTC's service delivery model and assess current genetic testing ordering practices by non-genetics providers.

Finally, this study was performed on a limited sample at one institution, making the results non-generalizable to other institutions, especially as this is a novel service delivery model. Further studies can assess differences in genetic testing outcomes between non-genetic providers and genetics providers at other institutions.

3.4.6 Future Directions

Future studies should continue to assess differences in genetic testing outcomes between non-genetic patients and genetic patients. As genetic testing is becoming both more commonplace and complex, understanding current genetic testing ordering practices and procedures by non-

genetics providers can allow for appropriate interventions by genetics professionals, including providing or creating educational resources, consulting services, standard operating procedures, formulary review, and new service delivery models, as determined by the needs of the institution and its patients. Based on the current success of the GTC and these results highlighting the success, the GTC is setting up satellite clinics and UPMC aims to create a similar model for adult clinics.

Additionally, patient satisfaction was not assessed in this study. It would be worth understanding if patients who receive comprehensive pre-test counseling by the GTC have higher satisfaction and understanding of results, compared to if genetic testing is ordered by the non-genetics provider, with whom they may have a long standing relationship.

3.5 Conclusion

The GTC is a novel service delivery model in that it provides UM; access to genetic counseling in a timely manner for routine and uncommon (but not medically complex) indications; comprehensive family history assessment; and a resource for non-genetics providers. The study found that the GTC provides significant benefit in pre- genetic test outcomes, including pre-test counseling, comprehensive family history assessment, UM for appropriate test selection, and a faster time from appointment to insurance pre-authorization submission, to patients. While the GTC does not have any significant differences in post-tests outcomes for patients undergoing genetic testing, it is available for post- genetic test counseling, which can be beneficial to the patient and provider, but was not assessed in this study. Other institutions should consider adoption of a service delivery model similar to the GTC to aid the genetic testing process, improve UM, and increase access to GCs.

4.0 Research Significance to Genetic Counseling and Public Health

Genetic testing is an expanding field that accounts for a significant amount of our healthcare dollars (UnitedHealth Center for Health Reform and Modernization, 2012). Genetic test results can be informative for treatment, management, and understanding of recurrence risk (Uhlmann et al., 2009). Furthermore, understanding the etiology of a disease or risk to manifest certain symptoms is imperative for early interventions, such as providing supportive therapies, increasing cancer surveillance, offering prenatal testing, prescribing different medications, or facilitating cascade testing. These interventions can be cost-saving to the healthcare system overall (D'Andrea et al., 2015). Therefore, it is a public health importance that the most appropriate genetic test is ordered for the patient.

However, the impact of genetic testing is only as good as the provider's understanding of genetic testing and the patient's access to genetic testing. Due to the increasing proportion of non-genetics providers ordering genetic testing, more inappropriate genetic testing is being ordered and less patient education is occurring (Armstrong et al., 2015; Baars et al., 2005; Bense et al., 2014; Diamonstein et al., 2018; Greendale & Pyeritz, 2001; Guttmacher et al., 2007; Harvey et al., 2007; Hofman et al., 1993; Klitzman et al., 2013; McGovern et al., 2003; Salm et al., 2014; Thurston et al., 2007). While many hospital systems and laboratories have implemented utilization management (UM) programs to aid test selection, which afforded significant cost savings and improved patient care, these programs do not necessarily increase access to genetic testing or genetic counseling (Anderson et al., 2012; Dickerson et al., 2014; Kotzer et al., 2014; Londre et al., 2017; Mathias et al., 2016; C. E. Miller et al., 2014; Riegert-Johnson et al., 2008; Riley et al., 2015; Suarez et al., 2017; Wakefield et al., 2018).

Access to genetic testing, with quality genetic counseling to understand the implications of genetic testing, has increased at Children’s Hospital of Pittsburgh, due to the recently implemented Genetic Testing Clinic (GTC). The GTC incorporates both UM and comprehensive genetic counseling services to provide both appropriate genetic test selection and thorough informed consent to non-genetics providers’ patients. This study highlighted the benefits to genetic testing ordered with the aid of the GTC compared to when it is ordered by a non-genetics provider. These benefits include utilization management, comprehensive family history assessment, thorough pre-test counseling, and the availability of post-test counseling. The GTC improves access to quality genetic counseling and ensures proper test selection – both of which are imperative to public health.

The Centers for Disease Control and Prevention (CDC) recognize 10 essential public health services (Center for Disease Control and Prevention, 2018). While this research incorporates all aspects of the 10 essential public health services, it especially addressed the “evaluation of effectiveness, accessibility, and quality of personal and population-based health services” (Center for Disease Control and Prevention, 2018). As the GTC is a new service delivery model, it was important to assess its benefits and possible limitations compared to genetic testing ordered by non-genetics providers.

This study highlights a novel service delivery model for genetic counseling services that incorporates UM. This service delivery model can be adopted or modified in other healthcare institutions to provide cost savings and increase patient care. Additionally, this study identified domains to modify protocols or increase education for non-genetics providers and their genetic testing ordering practices. These interventions will also allow for more appropriate test selection and provide quality patient care.

5.0 Public Health Essay: The Nuances of CPT® Coding for Multigene Panel Tests

5.1 Background

5.1.1 Insurance in the U.S.

Healthcare in the U.S. has been shaped by the private insurance market, with government sponsored insurance covering select populations (Starr, 2011). Insurance in the U.S. is complicated and is ever-evolving, but put simply, private insurance is purchased through an individual's employer or independently, providing insurance for individuals and families; Medicaid is a government sponsored program, providing insurance to individuals with low income or disabilities; and Medicare is a different government sponsored program, providing insurance to those over the age of 65. Kaiser Family Foundation (KFF) offers a comprehensive review of how insurance works, including the role of private insurance, Medicaid and its expansion through the Affordable Care Act (ACA), and Medicare (Antonisse et al., 2018; Kaiser Family Foundation, 2008, 2013, 2019). KFF also has a glossary of insurance related terms as well as a guide to understanding health insurance (Kaiser Family Foundation, n.d.-a, n.d.-b).

As opposed to universal healthcare in other Western countries, insurance in the U.S. is variable from plan to plan and can leave patients with a significant bill even when insured. The ACA mandated all insurance companies provide coverage for ten essential health benefits, including ambulatory patient services; emergency services; hospitalization; pregnancy, maternity, and newborn care; mental health and substance use disorder services; prescription drugs; rehabilitative and habilitative services and devices; laboratory services; preventive and wellness

services and chronic disease management; and pediatric services, including oral and vision care; however, additional services may be covered by the insurance company ("The Patient Protection and Affordable Care Act (PPACA)," 2010). Despite certain services being covered by an individual's insurance, patients are often responsible for out-of-pocket costs, in addition to the premium, due to co-insurance, co-pay, deductible, and/or the service being provided at an out-of-network facility.

5.1.1.1 Insurance and Genetic Testing

Genetic testing accounts for a significant portion of healthcare spending in the United States, and often provides incredibly valuable information for both medical professionals and families (UnitedHealth Center for Health Reform and Modernization, 2012). Informative genetic testing can guide healthcare management, allow for reproductive decision making, and provide an explanation for a health concern. However, genetic testing is not always a covered insurance benefit, and some insurances will only cover certain genetic testing. Prior authorization is often recommended or required to verify if genetic testing is a covered benefit.

To approve genetic testing, insurance companies typically require genetic testing results to impact medical management (such as medication change, reproductive decision making, etc.) (Aetna, 2019; BlueCross BlueShield of North Carolina, 2019). Insurance companies may have additional requirements, such as genetic counseling or the patient being at reproductive age, in order to authorize genetic testing (Aetna, 2019; Cigna, 2016; UnitedHealthCare, 2015; UPMC Health Plan, 2018). Therefore, it is imperative to include all appropriate information, often via a letter of medical necessity (LMN), when submitting for insurance authorization for genetic testing.

LMNs typically include patient's demographic and insurance information, provider and clinic information, the patient's ICD diagnoses, the name of the genetic test and laboratory it is

performed at, the genes included on the test, the CPT[®] code(s) associated with the test, and how the genetic testing results impact medical management (Uhlmann et al., 2017). These aspects of LMNs can be combined in conjunction with the clinic note and shared templates can be created to reduce the amount redundant work performed by the healthcare provider (Uhlmann et al., 2017).

GCs recognize the important role insurance plays in genetic testing. Genesurance is a recently coined term referring to the “portion of a genetic counseling session, whether intentional or non-intentional, that is devoted to the topic of costs and insurance/third party coverage (particularly for genetic testing)” (Brown et al., 2018). Research has examined both GC and patient perspectives of genesurance (Brown et al., 2018; Wagner et al., 2018). Brown et al. surveyed GCs about their genesurance practices and identified that 99% of clinical GCs spend some time on discussing genesurance during a clinical appointment, and the majority feel like it is important (87%) and a part of their job description (85%) (Brown et al., 2018). Relatedly, Wagner et al. surveyed patients on their expectation of a GC’s role regarding genesurance (Wagner et al., 2018). The study identified the majority of patients expect GCs to provide an estimated out-of-pocket expense (78%), know if a test is a covered benefit (77%), and to discuss this information during the appointment (75%) (Wagner et al., 2018). However, the multitude of insurance plans, various contracts with laboratories, thousands of genetic testing options, and inconsistent CPT[®] coding makes this a difficult task. Further, other medical providers do not typically go into the same detail of insurance coverage as GCs (Hooker et al., 2018).

5.1.2 Overview of Medical Coding

Insurance coverage for healthcare services is dictated by two coding systems: the World Health Organization’s (WHO’s) International Classification of Diseases (ICD) and US’s Current

Procedural Terminology (CPT®). The ICD code is the patient's diagnosis and the CPT® code is the procedure or service rendered.

5.1.2.1 ICD Coding

The ICD coding system was developed in 1893 when the International Statistical Institute charged a committee to create an international medical coding system to understand the epidemiology and statistics in deaths (Moriyama et al., 2011). The first iteration of ICD codes was known as the International List of Causes of Death and was rapidly adapted by many European and North American countries (Moriyama et al., 2011). These codes have been updated approximately every ten years, reflective of the latest understanding of medical diagnoses. The sixth iteration, ICD-6, entailed two major revisions with the addition of morbidity (medical diagnoses throughout life) instead of just mortality (causes of death) and changing the responsibility to maintain the coding from the United Nations to the World Health Organization (WHO) (Moriyama et al., 2011). Another major change occurred with the advent of ICD-10. Instead of utilizing a number-only organization system, ICD-10 utilizes an alpha numeric organization scheme to classify the body location, manifestation, and etiology of the disease, where the letter represents the body system, and the numbers denote details of the disease; this system allows for 14,000 different codes to exist, with further modifications by individual countries allowing for even more codes (Moriyama et al., 2011).

The WHO heeds users that ICD diagnosis codes are suitable for statistical and epidemiological studies, not billing purposes (World Health Organization, 1989). The U.S. realized that while ICD codes were useful for epidemiologic monitoring, they were lacking in clinical needs of the current billing structure of insurance. To address this need, the National Center for Health Statistics and the Council on Clinical Classifications joined forces to develop clinical

modifications (CM) to the ICD-9 scheme, creating ICD-9-CM (National Center for Health Statistics and Health Care Financing Administration, 1979). The clinical modifications allow for additional use of medical coding, including “indexing of medical records, medical care review, and ambulatory and other medical care programs” (National Center for Health Statistics and Health Care Financing Administration, 1979). Other countries have made similar modifications to reflect their need for medical record indexing and reimbursement (Moriyama et al., 2011).

Iterations of ICD-10 are currently in use, as it was released in the early 1990s (World Health Organization, 1989). The U.S. adopted ICD-10 for its death certificates in 1999; however, ICD-10 was not implemented in the U.S. until clinical modifications were complete to create the ICD-10-CM diagnosis coding (Center for Disease Control and Prevention, n.d.). The transition from ICD-9-CM to ICD-10-CM was required for U.S. Health Insurance Portability and Accountability Act (HIPAA) healthcare providers by October 1, 2015, after four years of postponement (Center for Disease Control and Prevention, n.d.; Health and Human Services, 2009). Additionally, there was the creation procedure coding system (PCS) modifications, ICD-10-PCS, for inpatient procedures (Center for Disease Control and Prevention, n.d.). The latest edition of ICD diagnosis coding, ICD-11, was developed in June 2018 with plans of implementation in June 2022 (World Health Organization, n.d.).

5.1.2.2 CPT® Coding

Similar to ICD coding, CPT® coding had origins other than medical billing. A review of CPT® coding was written by Dotson, but is also reviewed in this document (Dotson, 2013). In 1966, the American Medical Association (AMA) developed CPT® coding as a shorthand way to denote procedures performed, mainly surgeries, in the patient’s medical record (American Medical Association, n.d.). In the 1970s, these codes were updated to reflect other procedures and

implemented the five-digit numerical code still used today. CPT® codes were adopted for billing purposes in 1983 when Centers for Medicare and Medicaid Services (CMS) wanted to replace their billing code system of Healthcare Common Procedure Coding System (HCPCS) with CPT® billing codes for Medicare Part B claims (American Medical Association, n.d.). Throughout the 1980s, CPT® billing codes were adapted for Medicaid claims and outpatient surgical procedures, and the coding system was adapted by all HIPAA healthcare providers by October 2003 (American Medical Association, n.d.).

Currently, there are about 10,000 CPT® codes, and they are reviewed three times a year by the CPT® Editorial Panel, consisting of 17 doctors and experts from the AMA and other relevant organizations; during this process, codes are updated, removed, and added (American Medical Association, 2014). New codes suggested by healthcare providers, professional societies, or other parties are considered for addition, and the process from proposal to implementation takes approximately two to three years (American Medical Association, 2013; CPT® Editorial Panel, n.d.).

There are four main categories of CPT® codes: Category I, Category II, Category III, and Proprietary Laboratory Analyses (PLA) codes (CPT®, 2018). Category I codes consist of established procedures, such as surgeries, lab work, or radiology. Category II codes are supplemental tracking codes and are optional and used for quality measurements instead of billing purposes. Category III codes are for new procedures that do not quite meet Category I criteria and are tracked for assessment and outcomes of the procedure. Finally, PLA codes are a recent addition to the CPT® codes; PLAs are CPT® codes for proprietary procedures performed by a single source or multiple licensed facilities for tests such as genetic testing, advanced diagnostic laboratory tests, and clinical diagnostic laboratory tests (CPT®, 2018).

While insurance companies have a variety of services they will cover, the patient's ICD diagnosis needs to match the CPT® services provided. For example, a patient with acute appendicitis without abscesses, ICD-10-CM code K35.20, would undergo an appendectomy, CPT® code 44950; however, if a patient's medical record was coded with the diagnosis of unspecified abdominal pain, R10.9, an appendectomy would not be covered, as the diagnosis code does not reflect an appropriate reason as to why the appendix was removed. For genetics, ICD-10-CM code F82, denoting developmental delay, would be an appropriate diagnosis to undergo a SNP chromosomal microarray, CPT® code 81229, according to some payer coverage policies.

5.1.2.3 CPT® Coding for Genetic Testing

Accurate CPT® coding for genetic testing is complicated by there being over 75,000 genetic tests and approximately only 200 genetic testing specific CPT® codes (Concert Genetics, 2018; CPT®, 2018). Historically, genetic testing was coded on what was being performed on the sample – cell lysing, DNA extraction, PCR, interpretation, etc. The problem with this system was two-fold. First, different labs have different procedures for the same test, causing a different number of codes to be billed for. Using Medicare's Clinical Laboratory Fee Schedule, a lab's combination of CPT® codes for a 32-mutation *CFTR* analysis could cost anywhere from \$180.22 to \$516.22 due to the possible variations in coding and reimbursement (Logue, 2003). A similar, but not as disparate, analysis was also reported for *KRAS* assessment (Carlson, 2010). The second problem was that insurance companies did not know what they were paying for; all other laboratory CPT® codes were specific enough to allow the insurer to understand what was specifically performed. Many organizations, including the Department of Health and Human Services and AMP, recognized this coding problem, and the AMA developed a new, analyte-specific, two tier system for genetic testing CPT® codes (Association for Molecular Pathology,

2009; CPT®, 2018; S. Wright, 2012). Within Category I are two tiers of codes for genetic testing and molecular pathology (MoPath Codes). Tier I provides codes for testing of single genes or commonly ordered tests and Tier II includes catchall codes based on complexity of the test, ranging from identifying a single nucleotide variant to assessing 50 or more exons.

While each of the Tier I codes can only be billed once, Tier II codes and the miscellaneous 81479 code can be billed for multiple times with the use of modifiers. For example, 81479x4 means that code is performed (and billed) four times. Therefore, a genetic test can have multiple, separate Tier I codes and multiple Tier II and 81479 codes (with or without modifiers).

As with all CPT® codes, some modifications of genetic-specific codes have been made, and **Table 7** represents a sample of current (as of May 2019), commonly used genetic testing CPT® codes.

Table 7. Examples of genetic testing specific CPT® codes

CPT® code	Descriptor
Tier I: Single Gene	
81220	<i>CFTR</i> common variants (e.g., ACMG/ACOG guidelines)
81221	<i>CFTR</i> known familial variants
81222	<i>CFTR</i> duplication/deletion variants
81223	<i>CFTR</i> full gene sequence
81224	<i>CFTR</i> intron 8 poly-T analysis
81243	<i>FMRI</i> evaluation to detect abnormal (e.g., expanded) alleles
81244	<i>FMRI</i> characterization of alleles (e.g., expanded size and promoter methylation status)
Tier I: Multigene	
81228	Cytogenomic microarray analysis; interrogation of genomic regions for copy number variants
81229	Cytogenomic microarray analysis; interrogation of genomic regions for copy number variants and SNP
81415	Exome sequence analysis
81416	Exome sequence analysis, each comparator exome (e.g., parents, siblings)

Table 7 Continued

81425	Genome sequence analysis
81460	Whole mitochondrial genome sequencing, including heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel, including heteroplasmy detection
81440	Nuclear encoded mitochondrial genes sequence panel, must include analysis of at least 100 genes, including <i>BCSL1</i> , <i>C10orf2</i> , <i>COQ2</i> , <i>COX10</i> , <i>DGUOK</i> , <i>MPV17</i> , <i>OPA1</i> , <i>PDSS2</i> , <i>POLG</i> , <i>POLG2</i> , <i>RRM2B</i> , <i>SCO1</i> , <i>SCO2</i> , <i>SLC25A4</i> , <i>SUCLA2</i> , <i>SUCLG1</i> , <i>TAZ</i> , <i>TK2</i> , and <i>TYMP</i>
81410	Aortic dysfunction or dilation genomic sequence analysis panel, must include sequencing of at least 9 genes, including <i>FBN1</i> , <i>TGFBR1</i> , <i>TGFBR2</i> , <i>COL3A1</i> , <i>MYH11</i> , <i>ACTA2</i> , <i>SLC2A10</i> , <i>SMAD3</i> , and <i>MYLK</i>
81411	Aortic dysfunction or dilation duplication/deletion analysis panel, must include analyses for <i>TGFBR1</i> , <i>TGFBR2</i> , <i>MYH11</i> , and <i>COL3A1</i>
81413	Cardiac ion channelopathies genomic sequence analysis panel, must include sequencing of at least 10 genes, including <i>ANK2</i> , <i>CASQ2</i> , <i>CAV3</i> , <i>KCNE1</i> , <i>KCNE2</i> , <i>KCNH2</i> , <i>KCNJ2</i> , <i>KCNQ1</i> , <i>RYR2</i> , and <i>SCN5A</i>
81414	Cardiac ion channelopathies duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including <i>KCNH2</i> and <i>KCNQ1</i>
81439	Hereditary cardiomyopathy sequence analysis panel, must include sequencing of at least 5 cardiomyopathy related genes
81430	Hearing loss sequence analysis panel, must include sequencing of at least 60 genes, including <i>CDH23</i> , <i>CLRN1</i> , <i>GJB2</i> , <i>GPR98</i> , <i>MTRNR1</i> , <i>MYO7A</i> , <i>MYO15A</i> , <i>PCDH15</i> , <i>OTOF</i> , <i>SLC26A4</i> , <i>TMC1</i> , <i>TMPRSS3</i> , <i>USH1C</i> , <i>USH1G</i> , <i>USH2A</i> , and <i>WFS1</i>
81431	Hearing loss duplication/deletion analysis panel, must include copy number analyses for <i>STRC</i> and <i>DFNB1</i> deletions in <i>GJB2</i> and <i>GJB6</i> genes
81442	Noonan spectrum disorders sequence analysis panel, must include sequencing of at least 12 genes, including <i>BRAF</i> , <i>CBL</i> , <i>HRAS</i> , <i>KRAS</i> , <i>MAP2K1</i> , <i>MAP2K2</i> , <i>NRAS</i> , <i>PTPN11</i> , <i>RAF1</i> , <i>RIT1</i> , <i>SHOC2</i> , and <i>SOS1</i>
81470	X-linked intellectual disability sequence analysis panel, must include sequencing of at least 60 genes, including <i>ARX</i> , <i>ATRX</i> , <i>CDKL5</i> , <i>FGD1</i> , <i>FMR1</i> , <i>HUWE1</i> , <i>IL1RAPL</i> , <i>KDM5C</i> , <i>L1CAM</i> , <i>MECP2</i> , <i>MED12</i> , <i>MID1</i> , <i>OCRL</i> , <i>RPS6KA3</i> , and <i>SLC16A2</i>
81471	X-linked intellectual disability duplication/deletion gene analysis, must include analysis of at least 60 genes, including <i>ARX</i> , <i>ATRX</i> , <i>CDKL5</i> , <i>FGD1</i> , <i>FMR1</i> , <i>HUWE1</i> , <i>IL1RAPL</i> , <i>KDM5C</i> , <i>L1CAM</i> , <i>MECP2</i> , <i>MED12</i> , <i>MID1</i> , <i>OCRL</i> , <i>RPS6KA3</i> , and <i>SLC16A2</i>

Tier II: Miscellaneous

81400	Molecular pathology procedure, Level 1 analysis
81401	Molecular pathology procedure, Level 2 analysis
81402	Molecular pathology procedure, Level 3 analysis
81403	Molecular pathology procedure, Level 4 analysis

Table 7 Continued

81404	Molecular pathology procedure, Level 5 analysis
81405	Molecular pathology procedure, Level 6 analysis
81406	Molecular pathology procedure, Level 7 analysis
81407	Molecular pathology procedure, Level 8 analysis
81408	Molecular pathology procedure, Level 9 analysis
81479	Unlisted molecular pathology procedure

Adapted from (American Medical Association, 2018)

While these specific CPT[®] codes exist, there is room for interpretation by the genetic testing laboratory on how they denote their testing options. A health policy expert noted that comprehensive *BRCA1/2* sequencing, deletion/duplication, and rearrangement testing can be coded three ways, to lead to three different CMS reimbursement charges; however, these reimbursement rates vary by contracts and fee schedules (Quinn, 2017). The first, most intuitive way, uses the comprehensive code 81162 with a charge of \$1,615; however, the charge can be increased to \$2,948 using codes 81211 (*BRCA1/2* sequencing and deletion/duplication) and 81213 (uncommon deletion/duplications) or lowered to \$813 using codes 81214 (*BRCA1* sequencing and deletion/duplication), 81216 (*BRCA2* sequencing and deletion/duplication), and 81213 (Quinn, 2017). In a webinar, Dunn, a GC with an insurance company, argues that while panels do cost less from a technology perspective, they often cost more due to coding inefficiencies (Hooker et al., 2018).

Furthermore, there are problems with the 81479 code and the tier II codes. Tier II codes, including the miscellaneous 81479, lack the specificity of what test is actually performed to accurately bill for these services. While these codes were created with the intent to increase transparency on what is test is performed, there are currently no guidelines on how to code for multigene panels. This leaves the interpretation to the individual labs, which causes many

differences in coding for similar multigene panels. However, despite what coding the laboratory selects, the billing entity can modify which codes they chose to bill for through insurance.

5.1.3 Review of Epilepsy and Genetics

Epilepsy is a relatively common neurological condition, with a lifetime prevalence of 7.6 per 1,000 individuals worldwide (Fiest et al., 2017), affecting approximately 3.5 million individuals in the U.S. (Center for Disease Control and Prevention, 2019). The International League Against Epilepsy (ILAE) defines epilepsy as “a disease of the brain defined by any of the following conditions: at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; or diagnosis of an epilepsy syndrome” in 2014 (Fisher et al., 2014). In 2017, ILAE updated their operational classification of seizures: seizures can be either focal onset, generalized onset, or unknown onset; can be motor (ex. tonic-clonic) or non-motor (ex. absence); and can impair awareness or not (Fisher et al., 2017). Additionally, ILAE recognizes six different etiologic categories of epilepsy, of which multiple can be explanatory of a patient’s epilepsy (Falco-Walter et al., 2018). Epilepsy can be caused by a structural aberration, a genetic explanation, an infection, metabolic derangement, auto-immune disease, unknown, or a combination of these (Falco-Walter et al., 2018).

Many review articles on genetics and epilepsy are present in the literature and are discussed in this paper (El Achkar et al., 2015; Hildebrand et al., 2013; Pal et al., 2010; Poduri et al., 2014; Ream & Patel, 2015; Sands & Choi, 2017; Sisodiya, 2015; Thomas & Berkovic, 2014).

Historically, most epilepsy was considered idiopathic; however, recent advances in genetics has elucidated the role of single gene disorders, chromosomal aberrations, and polygenetic risk factors as a significant portion of causes of epilepsy. While the epidemiology of genetic-caused epilepsy is not exactly known, it is estimated that approximately one-third of epilepsy diagnoses have a strong genetic component, with another one-quarter of diagnoses having modifier and susceptibility alleles as contributing factors (Thomas & Berkovic, 2014). Genetics has a stronger likelihood to be contributory to a patient's epilepsy if there is a family history of seizures, younger age of onset, more severe presentation, certain brain MRI findings, and if other causes, such as infection, auto-immune disease, and trauma, are ruled out (Berg et al., 2017; Lindy et al., 2018; Sands & Choi, 2017). Additionally, these factors can guide the differential diagnosis and genetic testing selection. However, family history assessment of epilepsy and development of a differential diagnosis is complicated by genetic and phenotypic heterogeneity, reduced penetrance, variable expressivity, and *de novo* variants. *SCN1A* is the most common genetic cause of epilepsy, and accounts for a spectrum of different epilepsy conditions, including generalized epilepsy with febrile seizures plus (GEFS+), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial seizures, myoclonic astatic epilepsy (MAE), severe myoclonic epilepsy in infancy (SMEI) or Dravet Syndrome (DS), and simple febrile seizures (I. Miller & Sotero de Menezes, 2019). Some of the more common genetic epilepsy conditions are presented in **Table 8**.

Table 8. Common genetic epilepsy syndromes

Gene(s)/chromosomal region*	Name of Condition
15q11-q13, <i>UBE3</i>	Angelman Syndrome
1p36	Chromosome 1p36 deletion syndrome
<i>CHD2, GABRA1, HCN1, PCDH19, SCN1A, SCN1B, SCN9A, STXBPI</i>	Dravet Syndrome
<i>ARX, CDKL5, KCNQ2, SLC25A22, STXBPI</i>	Early infantile epileptic encephalopathy
<i>SCN1A, SCN9A</i>	Generalized epilepsy with febrile seizure plus (GEFS+)
<i>SLC2A1</i>	Glucose transporter type 1 deficiency syndrome
17p13.3	Miller-Dieker Syndrome
<i>MECP2</i>	Rett Syndrome
Chromosome 20	Ring chromosome 20
<i>TSC1, TSC2</i>	Tuberous Sclerosis Complex

Adapted from (El Achkar et al., 2015; Hildebrand et al., 2013; Lindy et al., 2018; Pal et al., 2010; Poduri et al., 2014; Ream & Patel, 2015; Thomas & Berkovic, 2014)

*Genes may be listed multiple times due to the genetic heterogeneity of having multiple associated conditions

5.1.3.1 Multigene Epilepsy Panels

Currently, there are no professional guidelines on genetic testing for epilepsy, but literature suggests comprehensive, multi-gene epilepsy panels are an appropriate first-tier test for many individuals who have a diagnosis of epilepsy (Berg et al., 2017; Levenson, 2017; Lindy et al., 2018). Comprehensive, multi-gene epilepsy panels are beneficial as they have a relatively high diagnostic yield, are able to assess many genetic epilepsy conditions, and may lead to actionable results.

In one genetic testing laboratory, patients with epilepsy received a genetic diagnosis 15.4% (1315/8565) of the time (Lindy et al., 2018). Of these genetic explanations, the majority (90%) were due to a sequencing change while only 9% were due to a copy number variant (Lindy et al., 2018). A prospective observational study of children with Early-Life Epilepsy (epilepsy diagnosed

before the age of 3) found epilepsy panels had higher diagnostic yield (27%, 31/114) compared to chromosomal microarrays (17%, 32/188) (Berg et al., 2017). While whole exome sequencing does have a higher diagnostic yield (33%, 11/33) (Berg et al., 2017), another study found that due to the high cost of exomes, epilepsy panels have the best cost-effective diagnostic yield (Sanchez Fernandez et al., 2019). The cost-benefit analysis also indicated that chromosomal microarrays would be the best cost-effective diagnostic yield if it costs less than \$1,267 (Sanchez Fernandez et al., 2019). Alternatively, if the patient has epilepsy and intellectual disability, developmental delay, multiple congenital anomalies, or dysmorphic features, a chromosomal microarray may have better diagnostic yield compared to a multi-gene epilepsy panel, but the cost-effectiveness was not studied (El Achkar et al., 2015; D. T. Miller et al., 2010).

Epilepsy is a condition with significant genetic and phenotypic heterogeneity. Even if the epilepsy syndrome fits a certain phenotype, such as infantile epilepsy, the patient may have a genetic diagnosis in a gene not traditionally associated with their presentation of symptoms. Additionally, the NGS platform allows for moderately sized panels to have a similar cost to larger panels. Therefore, more genes can be assessed and more actionable differential diagnoses can be ruled in or out, thus guiding management. A possible drawback to a broader panel, however, is a higher likelihood of receiving a VUS.

Finally, understanding if epilepsy has a genetic etiology can guide treatment and management, as some genes provide actionable results. For example, individuals with Glucose Transporter Deficiency Type I, caused by a pathogenic variant in *SLC2A1*, can often effectively manage their seizures and other manifestations with a ketogenic diet (Klepper et al., 2005); individuals with Pyridoxine-Dependent Epilepsy, caused by biallelic pathogenic variants in *ALDH7A1*, are treated with pyridoxine supplements (Basura et al., 2009); and individuals with

certain *POLG* pathogenic variants should avoid valproic acid as a seizure medication as it can cause liver disease or failure (Saneto et al., 2010). Additionally, if genetic test results do not yield a diagnosis, a provider is able to rule out many conditions that could have changed management.

5.1.3.2 Call for Multigene Epilepsy Panel CPT® Coding

Currently, there is no designated CPT® code for multi-gene epilepsy panels. Epilepsy, with a lifetime prevalence of 7.6 in 1000, is more common than cardiomyopathy (US prevalence 1 in 500 adults), X-linked intellectual disability (prevalence 1 in 600 males), inherited arrhythmias (prevalence 1 in 2000), and mitochondrial diseases (prevalence 1 in 5000 adults), which do have a panel specific CPT® code; therefore, it would be appropriate for epilepsy panels to have their own CPT® code (Center for Disease Control and Prevention, 2015; Fiest et al., 2017; McKenzie et al., 2016; Ng & Turnbull, 2016; P. J. Schwartz et al., 2009). Through creation of an epilepsy multi-gene panel CPT® code, standards for a minimum gene list would be established, insurance companies would have an accurate understanding of testing performed, laboratories would be able to more accurately bill for their services, and patient outcomes may improve.

While insurance coverage for genetic CPT® codes varies significantly by plan, transparent coding with the creation of a multigene epilepsy sequencing panel CPT® code will allow for correct patient billing, accurate reimbursement, and create a standard for genetic testing laboratories. With thousands of different genetic tests, but only a couple hundred CPT® codes, it is impossible for consistent and customary billing (Concert Genetics, 2018; CPT®, 2018). This lack of transparency in CPT® coding may lead to insurance denying the test, causing the patient to either have a significant bill or not be able to access the service, or if the insurance approves the test, the insurance may over pay or under pay for the test due the lack of consistent CPT® codes.

5.1.4 Specific Aims

5.1.4.1 Specific Aim 1

To determine CPT[®] coding and genes included on epilepsy sequencing panels at various genetic testing laboratories.

5.1.4.2 Specific Aim 2

To propose standards for CPT[®] coding for multigene epilepsy sequencing panels.

5.2 Methods

5.2.1 Current CPT[®] Coding of Epilepsy Multigene Sequencing Panels

The current landscape of CPT[®] coding for epilepsy multigene sequencing panels at commercial genetic testing laboratories in the U.S. was assessed. Genetic testing laboratories included in this study were determined by search results identified via Concert Genetics (formerly NextGxDx), a website and technology company that assists with transparency and navigation of genetic testing (Concert Genetics, n.d.). Concert Genetics groups genetic tests by similar indications and if they are single-target or panel testing to allow for side-by-side comparisons (Concert Genetics, n.d.). Genetic tests listed in the category “Epilepsy and Seizure Disorder Panel Tests” were reviewed, and laboratories were included if they were commercial, U.S. based, and offered at least one epilepsy sequencing panels.

Once laboratories were identified, their websites were interrogated for their offerings of epilepsy sequencing panels. Tests were identified in two ways: the search box and neurology/epilepsy specific test menus. First, the words “epilepsy”, “epileptic”, and “seizure” were searched, and results were read to identify multigene sequencing panels with one of the aforementioned words in the test name. Similarly, if the laboratory website had a neurology specific or epilepsy specific test menu or webpage, the tests were read to identify multigene sequencing panels with one of the aforementioned words in the test name. Tests were excluded if they were offered on a research basis.

Next, the test page was read to identify the genes included on the panel and the CPT® codes for the test. If the CPT® codes or gene lists were not available on the website, a phone call was made to the lab’s customer service to obtain this information.

The variables, including lab, test, genes, and CPT® codes, were assessed using descriptive statistics to understand trends in multigene epilepsy sequencing panels. Statistical analyses were completed using GraphPad Prism (v. 8, San Diego, CA).

5.2.2 Proposed CPT® Code for Epilepsy Multigene Sequencing Panels

There is no background literature on how the minimum gene lists were determined for already established multigene panel CPT® codes. However, reasonable inclusion criteria for a minimum gene list are relatively common etiologies of genetic epilepsy and genes that have actionable results. Therefore, the inclusion criteria for the proposed CPT® Code for Epilepsy Multigene Sequencing Panels is represented in **Table 9**. The inclusion criteria were determined by reviewing the prevalence of genes included on current CPT® codes for multigene panels. A brief review of literature yielded most genes had a prevalence less than 1:100,000; however, some genes

were rarer, such as *TAZ* (1:140,000), *HRAS* (1:230,00), and *WFS1* (1:550,000) (Abe et al., 2011; Barrett et al., 1995; Clarke et al., 2013). For epilepsy genes where prevalence was established, the prevalence was compared to the proportion of patients who had a pathogenic sequencing variant in a specific gene within a cohort of individuals with genetic epilepsy based on Lindy et al., which estimates 1:100,000 is approximately equal to 3% of patients with a pathogenic sequencing variant in a specific gene within a cohort of individuals with genetic epilepsy (Lindy et al., 2018). There is a genetic etiology for epilepsy approximately 25% of the time, which represents the 0.75% of patients with an epilepsy condition due to a pathogenic sequencing variant in a specific gene within a cohort of individuals with epilepsy. If a treatment was available, the criterion was scaled to include rarer genes.

A literature review for the prevalence and treatment of genetic epilepsy was performed. Genes that were identified to be present in 12 or more (20%) panels were investigated. Peer-reviewed literature was read to determine the prevalence and specific treatment (if available) for each of the genes. Due to the possibility of isolated ethnic groups having a high prevalence due to the founder effect, genes were included if the prevalence was determined in multiple ethnic groups or a multi-ethnic study. If there was no peer-reviewed literature on the gene's prevalence it was excluded, as this likely represents a lower prevalence. It is possible for a gene to meet one criterion but fail another; these genes are included due to the ease of multigene sequencing on NGS platforms. The proposed minimum gene list for the CPT[®] code is based on the genes that met the inclusion criteria based on the literature review performed.

Table 9. Inclusion criteria of genes for proposed CPT® code for epilepsy multigene sequencing panel

Inclusion criteria
Prevalence of at least 1:100,000 of an epilepsy condition due to a pathogenic sequencing variant in a specific gene OR
Prevalence of at least 1:150,000 of an epilepsy condition due to a pathogenic sequencing variant in a specific gene AND actionable results for treatment or agents to avoid OR
Prevalence of at least 0.75% of an epilepsy condition due to a pathogenic sequencing variant in a specific gene within a cohort of individuals with epilepsy OR
Prevalence of at least 0.5% of an epilepsy condition due to a pathogenic sequencing variant in a specific gene within a cohort of individuals with epilepsy AND actionable results for treatment or agents to avoid
Prevalence of at least 3% of an epilepsy condition due to a pathogenic sequencing variant in a specific gene within a cohort of individuals with genetic epilepsy OR
Prevalence of at least 2% of an epilepsy condition due to a pathogenic sequencing variant in a specific gene within a cohort of individuals with genetic epilepsy AND actionable results for treatment or agents to avoid

5.3 Results

5.3.1 Current CPT® Coding of Epilepsy Multigene Sequencing Panels

Concert genetics identified 128 different genetic tests in the category “Epilepsy and Seizure Disorder Panel Tests”. These tests are offered by 27 different laboratories, of which eight were excluded. Four labs were excluded as they are passthrough laboratories, two labs were excluded as they are not commercially available, one was excluded as it was not US-based and one was excluded as it was Direct to Consumer testing. The remaining 19 labs were included in the analysis.

These 19 labs offer 63 NGS-based multigene epilepsy panels, as outlined in **Table 10**. All the information was available online, with the exception of CPT® codes for five laboratories where

calls were made. Of note, all panels are unique, with the exception of an identical seven-gene epilepsy and migraine panel offered by two different laboratories; however, different CPT[®] coding was used.

Table 10. Overview of dataset

Variable	n (standard deviation) [range]
Labs	19
Different panels	63
Small panel (39 genes or less)	20
Medium panel (40-99 genes)	20
Large panel (100+ genes)	23
Mean tests/lab	3.3 (2.5) [1-9]
Mean number of genes on panel	129 (213) [7-1501]
Mean number of CPT [®] codes/test	4.2 (3.4) [1-14]
Mean number of Tier I codes/test	1.0 (0.2) [0-6]
Mean number of Tier II codes/test	2.6 (2.8) [0-7]
Mean number of 81479 codes/test	0.6 (0.5) [0-1]
Mean number of genes/CPT [®] code	30.6 (92.5) [1.8-595]
Mean number of CPT [®] modifiers/test	33.3 (105.8) [1-628]
Mean number of Tier I modifiers/test	1.0 (1.4) [0-6]
Mean number of Tier II modifiers/test	7.8 (15.2) [0-96]
Mean number of 81479 modifiers/test	24.5 (92.7) [0-567]
Mean number of genes/CPT [®] modifier	3.9 (90.6) [0.5-595]

There were a total of 1577 different genes included on these panels. No gene was present in all panels, however, *SCN1A*, the most common genetic cause of epilepsy, was the most common gene in all the panels. Details of gene content in the panels is presented in **Table 11**.

Table 11. Gene content in panels

Count*	Gene(s)
50	<i>SCN1A</i>
46	<i>SLC2A1</i>
45	<i>SCN2A</i>
44	<i>FOLR1</i>
43	<i>CDKL5, POLG</i>
42	<i>GRIN2A, SCN1B</i>
41	<i>KCNT1, PCDH19, STXBP1</i>
39	<i>ALDH7A1, ARX, KCNQ2, MECP2, PNPO, SCN8A, TBC1D24</i>
38	<i>GABRA1</i>
37	<i>GABRG2, KCNQ3, KCTD7, PPT1</i>
36	<i>CHD2, CLN3, CLN5, CLN6, CLN8, MEF2C, MFSD8, TPPI, TSC1, TSC2</i>
35	<i>EPM2A, FOXG1, GABRB3, GAMT, NHLRC1, PRRT2, SPTAN1</i>
34	<i>ADSL, CSTB, CTSD, GOSR2, PNKP, SLC25A22, SLC9A6</i>
33	<i>CACNA1A</i>
32	<i>ARHGEF9, CNTNAP2, ZEB2</i>
31	<i>EEF1A2, GRIN2B, LGI1, MBD5, NRXN1, SCARB2, UBE3A</i>
30	<i>CHRNA2, CHRNA4, CHRN2, GRIN1, PLCB1, SLC6A8, SYNGAP1, TCF4, WDR45</i>
29	<i>SLC19A3</i>
28	<i>DNMI, GATM, SLC13A5</i>
27	<i>CASK, KCNB1, PIGA, PRICKLE1, WWOX</i>
26	<i>DEPDC5, GNAO1, HCN1, PURA, SCN9A, STX1B, SZT2</i>
25	<i>ALG13, KCNJ10, SLC35A2</i>
24	<i>ATPIA2, IQSEC2, KCNC1, ST3GAL5</i>
23	<i>DYRK1A</i>
22	<i>DNAJC5, KANSL1, PIGO, ST3GAL3</i>
21	<i>ASAHI, EFHC1, GABRB2, GLDC, HNRNPU, SLC6A1, SMC1A, SYNI</i>
20	<i>AMT, ATP6AP2, CLCN4, CTSF, FLNA, KCNA2</i>

*Genes that are on less than 20 different panels are not included in this table

Finally, laboratory-recommended CPT® codes varied drastically between panels. A full list of CPT® codes used is presented in **Table 12**.

Table 12. CPT® codes used

CPT® Code	CPT® Code Description	Number of panels in which code was used	Number of times code was used (modifiers)
Tier I Codes		66	66
81175	<i>ASXL1</i> Full Sequencing	1	1
81185	<i>CACNA1A</i> Full Sequencing	5	5
81189	<i>CSTB</i> Full Sequencing	10	10
81210	<i>BRAF</i> V600 Analysis	2	2
81290	<i>MCOLN1</i> Variant Analysis	1	1
81291	<i>MTHFR</i> Variant Analysis	1	1
81302	<i>MECP2</i> Full Sequencing	14	14
81304	<i>MECP2</i> Deletion/Duplication Analysis	7	7
81311	<i>NRAS</i> Variant Analysis	1	1
81321	<i>PTEN</i> Full Sequencing	2	2
81323	<i>PTEN</i> Deletion/Duplication Analysis	2	2
81330	<i>SMPD1</i> Variant Analysis	1	1
81415	Exome Sequencing	1	1
81443	Genetic testing for severe inherited conditions. Must include sequencing of at least 15 genes	15	15
81460	Whole mitochondrial genome sequencing, with heteroplasmy detection	1	1
81465	Whole mitochondrial genome large deletion analysis panel	1	1
Tier II Codes		63	490
81401	Level 2 analysis (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant, or detection of a dynamic mutation disorder/triplet repeat)	4	7
81403	Level 4 analysis (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)	17	24

Table 12 Continued

81404	Level 5 analysis (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)	30	98
81405	Level 6 analysis (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/ deletion variants of 11-25 exons)	34	125
81406	Level 7 analysis (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)	36	165
81407	Level 8 analysis (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/ deletion variants of > 50 exons, sequence analysis of multiple genes on 1 platform)	34	57
81408	Level 9 analysis (eg, analysis of > 50 exons in a single gene by DNA sequence analysis)	8	14
81479	Unlisted molecular pathology procedure	35	1544

5.3.2 Proposed CPT® Code for Epilepsy Multigene Sequencing Panels

Based on a review of the literature, 25 genes met the inclusion criteria for the proposed multigene epilepsy sequencing panel CPT® code: *ALDH7A1*, *CACNA1A*, *CDKL5*, *CHD2*, *GABRG2*, *GLDC*, *GRIN2A*, *KCNQ2*, *MECP2*, *PCDH19*, *POLG*, *PRRT2*, *SCN1A*, *SCN1B*, *SCN2A*, *SCN8A*, *SLC2A1*, *SLC9A6*, *STXBPI*, *SYNGAP1*, *TCF4*, *TPP1*, *TSC1*, *TSC2*, and *ZEB2*. However, the CPT® code could allow analysis of additional genes with the phrasing “must include sequencing of at least # genes, including...”. This list was determined based on the inclusion criteria in **Table 9**. The genes, condition, prevalence, and treatment are listed in **Table 13**.

Table 13. Proposed genes for multigene epilepsy sequencing panel CPT® code

Gene	Condition(s)	Estimated Prevalence	Specific Treatment
<i>ALDH7A1</i>	Pyridoxine-Dependent Epilepsy	1:20,000 ¹ – 1:100,000 ²	Pyridoxine ³
<i>CACNA1A</i>	Early Infantile Epileptic Encephalopathy, Type 42	0.9% of individuals with epilepsy ⁴	Acetazolamide ⁵
<i>CDKL5</i>	Early Infantile Epileptic Encephalopathy, Type 2	7.6% of individuals with genetic epilepsy ⁶ ; 1.8% of individuals with epilepsy ⁴	Ketogenic diet ⁷
<i>CHD2</i>	Childhood-onset Epileptic Encephalopathy	1.2% of individuals with epilepsy ⁸	—*
<i>GABRG2</i>	Generalized Epilepsy with Febrile Seizures Plus, Type 3; Early Infantile Epileptic Encephalopathy, Type 74; Familial Febrile Seizures, Type 8	3.6% of individuals with genetic epilepsy ⁶	—*
<i>GLDC</i>	Glycine Encephalopathy	1:90,000 ^{9,10}	Benzoate ¹¹⁻¹³ , NMDA receptor antagonist ^{11,12} , low protein diet ¹³ ; Avoid valproate ¹⁴
<i>GRIN2A</i>	<i>GRIN2A</i> -Related Speech Disorders and Epilepsy	2.4-3.2% of individuals with genetic epilepsy ^{4,6}	Avoid carbamazepine, barbiturates, and phenytoin ^{15,16}
<i>KCNQ2</i>	Early Infantile Epileptic Encephalopathy, Type 7; Benign Neonatal Seizures, Type 1	13.2% of individuals with genetic epilepsy ⁶ ; 1.8-2.9% of individuals with epilepsy ^{4,17}	Lacosamide ¹⁸
<i>MECP2</i>	Rett Syndrome	3.5% of individuals with genetic epilepsy ⁶	—*
<i>PCDH19</i>	Early Infantile Epileptic Encephalopathy, Type 9	5.7% of individuals with genetic epilepsy ⁶ 0.9% of individuals with epilepsy ⁶	—*
<i>POLG</i>	Alpers-Huttenlocher syndrome; Childhood myocerebrohepatopathy spectrum; Myoclonic epilepsy myopathy sensory ataxia	1:51,000 ¹⁹	Avoid valproic acid ²⁰
<i>PRRT2</i>	Familial Infantile Convulsions with Paroxysmal Choreoathetosis;	7.2% of individuals with genetic epilepsy ⁶	—*

Table 13 Continued

	Benign Familial Infantile Seizures, Type 2		
<i>SCN1A</i>	Dravet syndrome; Generalized epilepsy with febrile seizures plus; Intractable childhood epilepsy with generalized tonic-clonic seizures; Intractable infantile partial seizures; Myoclonic astatic epilepsy; Simple febrile seizures	1:15,000 ²¹ – 1:41,000 ²² ; 24.8% of individuals with genetic epilepsy ⁶ ; 3.6–4.4% of individuals with epilepsy ^{4,17}	Avoid carbamazepine ²³ , lamotrigine ²⁴ , vigabatrin ²⁵ , and phenytoin ²⁶
<i>SCN1B</i>	Generalized Epilepsy with Febrile Seizures Plus, type 1; Early Infantile Epileptic Encephalopathy, Type 52	1.2% of individuals with epilepsy ⁴	—*
<i>SCN2A</i>	Early Infantile Epileptic Encephalopathy, Type 11; Benign Familial Infantile Seizures, Type 3	7.4% of individuals with genetic epilepsy ⁶ ; 1.8% of individuals with epilepsy ^{4,17}	Sodium channel blocker if seizures before 3 months ²⁷
<i>SCN8A</i>	Early Infantile Epileptic Encephalopathy, Type 13; Benign Familial Infantile Seizures, Type 5	3.6% of individuals with genetic epilepsy ⁶ ; 1.5% of individuals with epilepsy ⁴	—*
<i>SLC2A1</i>	Glucose Transporter Type I Deficiency Syndrome	1:83,000 ²⁸ – 1:90,000 ²⁹ ; 3.2–3.6% of individuals with genetic epilepsy ^{4,6}	Ketogenic diet ³⁰
<i>SLC9A6</i>	Christianson Syndrome	1:16,000 – 1:100,000 ³¹	—*
<i>STXBP1</i>	STXBP1 Encephalopathy with Epilepsy	1:91,000 ³² ; 5.1% of individuals with genetic epilepsy ⁶ ; 1.2–2.7% of individuals with epilepsy ^{4,17}	—*
<i>SYNGAP1</i>	<i>SYNGAP1</i> -Related Developmental and Epileptic Encephalopathy	1.0% of individuals with epilepsy ¹⁰	—*
<i>TCF4</i>	Pitt-Hopkins Syndrome	1:11,000 ³³ – 1:41,000 ³⁴	—*
<i>TPP1</i>	Neuronal Ceroid Lipofuscinosis, Type 2	0.9% of individuals with epilepsy ⁴	—*
<i>TSC1</i>	Tuberous Sclerosis Complex	1:120,000 ^{35–37}	Vigabatrin ³⁸
<i>TSC2</i>	Tuberous Sclerosis Complex	1:43,000 ^{35–37} ; 2.3–3.2% of individuals with genetic epilepsy ^{4,6}	Vigabatrin ³⁸
<i>ZEB2</i>	Mowat-Wilson Syndrome	1:50,000 – 1:70,000 ³⁹	—*

References: 1. (Ebinger et al., 1999) 2. (Baxter et al., 1996) 3. (Basura et al., 2009) 4. (Butler et al., 2017) 5. (Battistini et al., 1999) 6. (Lindy et al., 2018) 7. (Lim et al., 2017) 8. (Carvill et al., 2013) 9. (Applegarth et al., 2000) 10. (Kure et al., 2006) 11. (Bjoraker et al., 2016) 12. (Korman et al., 2004) 13. (Hennermann et al., 2012) 14. (Hall & Ringel, 2004) 15. (Striano & Capovilla, 2013) 16. (Van Bogaert, 2013) 17. (Mercimek-Mahmutoglu et al., 2015) 18. (Schubert-Bast et al., 2017) 19. (Darin et al., 2001) 20. (Saneto et al., 2010) 21. (Wu et al., 2015) 22. (Brunklau et al., 2012) 23. (Horn et al., 1986) 24. (Guerrini et al., 1998) 25. (Ceulemans et al., 2004) 26. (Saito et al., 2001) 27.

(Wolff et al., 2017) 28. (Larsen et al., 2015) 29. (Coman et al., 2006) 30. (Klepper et al., 2005) 31. (Pescosolido et al., 2014) 32. (Stamberger et al., 2016) 33. (Whalen et al., 2012) 34. (Rosenfeld et al., 2009) 35. (Osborne et al., 1991) 36. (Jones et al., 1999) 37. (Au et al., 2007) 38. (Camposano et al., 2008) 39. (Mowat & Wilson, 2010)

* Peer reviewed literature search did not yield a specific treatment of choice

5.4 Discussion

5.4.1 Current CPT® Coding of Epilepsy Multigene Sequencing Panels

There is significant variety in content of multigene epilepsy sequencing panels, as well as significant variety in CPT® coding.

First, panels varied in gene content, ranging from as small as seven genes, to over 1500 genes. Panels were often divided into phenotypes, such as comprehensive testing, infantile epilepsy, childhood onset epilepsy, epileptic encephalopathy, epilepsy with migraines, myoclonic epilepsy, febrile epilepsy, focal epilepsy, and panels with actionable genes. Given the clinical and genetic heterogeneity of genetic epilepsy, though, it can be difficult to properly assess and diagnosis patients especially early on in their disease presentation when full symptomatology may not have completely evolved.

While common genes were noted in similar panels, only one set of panels had identical genes - an epilepsy with migraine panel; however, one lab only coded the panel with only one CPT® code, while the other lab coded the panel with six CPT® codes. This difference in coding of the same panel content is reflective of the highly variable interpretation of CPT® coding.

Other laboratories also differed in their interpretation of CPT® codes. PreventionGenetics has a 2:1 ratio of CPT® codes to gene, while Knight Molecular Diagnostics has a 1:1 ratio. All other labs tended to assign CPT® codes based on the analysis performed at large, instead of a gene

by gene approach. Through this approach, some labs had as few as one CPT[®] code per test, often using 81443 (genetic testing for severe inherited conditions) or 81479 (unlisted molecular pathology procedure). However, the AMA is working on a platform to provide clarity and recommended coding on a test by test basis (J. Vento, personal communication, June 3, 2019).

5.4.2 Proposed CPT[®] Code for Epilepsy Multigene Sequencing Panels

The review of literature for prevalence and treatment yielded 25 genes that met the criteria for the proposed CPT[®] code for epilepsy multigene sequencing panels. Already established CPT[®] codes for panel gene coverage requirements vary from as few as two genes for cardiac ion channelopathies duplication/deletion gene analysis panel to as many as 19 specific genes with analysis of at least 100 genes for a nuclear encoded mitochondrial genes sequence panel (American Medical Association, 2018). While the proposed 25 specific genes for an epilepsy multigene sequence CPT[®] code is more than what is required in already established CPT[®] codes, this more extensive gene requirement is potentially needed to account for the significant genetic heterogeneity of epilepsy.

The inclusion criteria for the genes was specifically based on the prevalence of an “epilepsy condition due to a pathogenic sequencing variant in a specific gene” as this CPT[®] code is for epilepsy multigene *sequencing* panels. A pathogenic sequencing variant accounts for about 90% of all epilepsies with a genetic etiology, with the remaining 10% due to a pathogenic copy number variant (CNV) or an imprinting aberration (Lindy et al., 2018). Of note, *UBE3A*, the gene associated with Angelman Syndrome, was excluded from the proposed gene list. While Angelman Syndrome has a high enough prevalence of 1:12,000 – 1:50,000, only 11% of Angelman Syndrome diagnoses are due to a sequencing variant (the majority are due to a methylation aberration which

cannot be identified on an NGS platform) (Fang et al., 1999; Malzac et al., 1998; Oiglane-Shlik et al., 2006; Steffenburg et al., 1996). Therefore, calculations estimate the prevalence of *UBE3A* pathogenic sequencing variants at about 1:109,000 – 1:455,000, which is not a high enough prevalence to justify its inclusion on the gene list.

5.4.3 Limitations

5.4.3.1 Current CPT® Coding of Epilepsy Multigene Sequencing Panels

The data collected for the current CPT® coding of epilepsy multigene sequencing panels is accurate as of May 2019; however, labs may change their CPT® codes at any time.

While differences in genetic testing laboratory CPT® coding practices were elucidated, the downstream effects of these differences on insurance company coverage and reimbursement and patient outcomes were not assessed. There is little public transparency by insurance companies on coverage of services. Furthermore, coverage of services varies significantly by insurance plan. Additionally, reimbursement is affected by contracts insurance companies have with different laboratories. Due to these complexities, cost and other related outcomes were not assessed.

Finally, epilepsy multigene sequencing panels are not the only genetic test that has inconsistent CPT® coding. These nuances in coding are present in other genetic tests but were not assessed as it would be beyond the scope of this project. Future projects should assess these nuances and propose standardized CPT® coding to increase consistency and improve transparency.

5.4.3.2 Proposed CPT® Code for Epilepsy Multigene Sequencing Panels

There are no evidence-based guidelines on how to determine a minimum gene list for a CPT® code. As such, an important limitation of this project was that this was an academic exercise

that did not account for expert opinion, which would be necessary before finalization of a proposed gene list. A reasonable guideline, though, is a relatively high prevalence of a pathogenic variant in genes associated with epilepsy with special considerations for genes that have actionability. Further consideration and literature review would need to be completed to identify additional genes that should be included on a proposed panel. Due to genetic conditions being rare, prevalence of these conditions can be estimated within a degree of magnitude, but accurate, specific prevalence rate is difficult to calculate. Therefore, it is likely that genes were included when the true prevalence of pathogenic sequencing variants is lower than the cutoff and that genes were excluded when the true prevalence of pathogenic sequencing variants is higher than the cutoff. As such, this proposed gene list should be used as a starting point for future work on developing a final minimum gene list for a CPT® code.

Additionally, the inclusion criteria were only based on the prevalence of conditions caused by a pathogenic sequencing variant that include an epilepsy phenotype. Given the variable expressivity of genetic conditions, a condition may have epilepsy as a phenotypic outcome in only a minority of cases. For example, *TCF4* was included on the gene list, but only about one-third of patients with Pitt-Hopkins Syndrome have epilepsy (de Winter et al., 2016). Future analyses should include the likelihood of epilepsy for each condition and could be considered for development of gene lists for CPT® codes.

As we understand more of prevalence of these conditions and the prevalence of epilepsy within these conditions, the gene list for all CPT® codes should be updated.

5.5 Conclusion

There are substantial differences in CPT® coding for multigene epilepsy sequencing panels. The lack of consistency affects laboratory reimbursement, insurance coverage, and patient care. Therefore, clear CPT® coding is imperative. The proposed gene list would provide a standard of care for multigene epilepsy sequencing panels and allow for more transparency for all stakeholders. This has public health significance as epilepsy affects millions of Americans and there is benefit of understanding the possible genetic role in the etiology of epilepsy for care and management. Therefore, it is imperative to provide access to more uniform genetic testing with consistent, transparent CPT® coding.

Appendix IRB Approval Letter

11/14/2018

<https://www.osiris.pitt.edu/osiris/Doc/0/17TNJRBR8S74D22QMJE8AO2ME6/fromString.html>

University of Pittsburgh Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.urb.pitt.edu>

Memorandum

To: Christine Munro
From: IRB Office
Date: 11/9/2018
IRB#: [PRO18060616](#)
Subject: Genetic Testing Outcomes of a Utilization Management Genetic Counseling Clinic compared to Genetic Testing Ordered by Non-Genetics Providers

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(5)

The IRB has approved a waiver of informed consent/HIPAA authorization to access, record and use protected patient health information/patient medical record information.

This study has been approved under 45 CFR 46.404 for the inclusion of children.

The risk level designation is Minimal Risk.

Approval Date: 11/9/2018
Expiration Date: 11/8/2019

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

<https://www.osiris.pitt.edu/osiris/Doc/0/17TNJRBR8S74D22QMJE8AO2ME6/fromString.html>

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